



Fig. 3. Case 2. Mrs. Charles G. Before X-ray treatment.

showed an entirely normal stomach with normal peristalsis and smooth mucosal relief.

The patient was seen again in February, 1931. She was very well and another radiological examination of the stomach was entirely negative. The last word had from the patient was in January, 1934; she was entirely well, as far as her stomach was concerned, but was treated by Dr. Francis Carter Wood for a tumor of the tonsil."

Case 3. "A man, aged fifty-nine years, was explored by Prof. Enderlen, Heidelberg, on June 23, 1929. A gastric carcinoma, the size of a fist, was found tightly adherent to the pancreas. Roentgenograms show plainly the extent of the tumor and its gradual regression. The patient was able to work as an engineer after being dismissed from the clinic in November, 1930. February 1, 1932, he was readmitted for a prophylactic series of roentgen treatments. On February 8, 1932, he suffered a sudden massive hematemesis; 2 liters of blood were vomited and the patient collapsed. He died a few hours afterwards. The post-mortem specimen showed only a few remnants of the carcinoma on the posterior gastric wall and a perforation into the splenic artery, from which the fatal hemorrhage occurred."

Dr. Charles Waters (9), Baltimore, Maryland, records an interesting case. He states as follows:

"I should like to record a case of gastric tumor which proved on exploration to be entirely inoperable. However, it was highly radio-sensitive and almost completely disappeared under irradiation. It subsequently proved to be a Grade III adeno-carcinoma. The second operation revealed only a small nodule in the pylorus which was resected by a Polya closure. The patient subsequently died an acute abdominal death and generalized abdominal metastasis was discovered. This case, however, proved one thing if nothing else and that is that a stomach which was completely involved by an unusual rubbery type of growth responded to irradiation and became entirely operable. The character of deeply seated abdominal malignant disease is often such as to defy every known method of scientific investigation. The time honored surgical exploration of the abdomen as the primary step in the treatment of abdominal masses of uncertain etiology and uncertain operability may, we believe, be obviated in some cases by pre-operative irradiation."

At one time there was relatively little hope for success in the treatment of carcinoma of the cervix of the uterus. Irradiation today has gone a long way toward dispelling this hopelessness. This may be no

basis for the hope of similarly brilliant results in the domain of gastro-intestinal irradiation, but certainly here is fertile field which may yield the unexpected.

Merrit, E. A. (10), in 1936 reported on a series of 13 cases treated since January, 1934. Three of these cases—25%—were living and apparently free of all evidence of disease, clinically and by X-ray examination. Most of the cases were in a dying condition when treated. The treatments were given daily except Sunday, using the modified Coutard technique. I will cite only one of Dr. Merrit's cases:

Case 3. "I. C., white male, aged seventy-two. Eight years previous to examination the patient fell off a horse and struck his side. He dates the onset of his trouble from that time. For the past seven months he has had indigestion. No nausea or vomiting. Fig. 5 shows extensive papillary carcinoma involving almost the entire body of the stomach. Wassermann was negative. From June 18, 1934, to July 14, 1934, the patient received 2,100 r to an area 20 x 20 cm. over the anterior stomach, 2,100 r to an area 20 x 20 cm. over the posterior stomach and 600 r to an area 20 x 20 cm. over the lateral stomach with the following factors: 220 kv. (peak), 20 ma., 50 cm. distance, Thoraeus tin filter equivalent to 2 mm. copper. The tumor dose was 1,700 r. The initial treatments were 100 r; these were lengthened after a few days until each area was receiving 250 r in rotation, only a single area being treated daily. Patient was not nauseated nor did he vomit at any time during or after treatment. Roentgen examination of the stomach two months after treatment showed considerable improvement. There was still, however, evidence of malignancy on the posterior wall. There was a dry desquamation of the skin. The stomach was washed and the centrifuged material was studied by Dr. J. W. Lindsay who reported papillary carcinoma on several fragments. In spite of the previous intensive therapy, it was decided to give the patient a second series of roentgen therapy, more intensive than the first. To save the skin and improve the depth dose a tin filter equivalent to 5 mm. copper was used. Six months after the first series the patient received 3,000 r (measured in air) to each of the three 20 x 20 cm. areas, or a total of 9,000 r in forty-two days with the following factors: 220 kv., (peak), 20 ma., 50 cm. distance, 250 r daily, 25 minutes, with 1.25 mm. tin, 0.25 mm. copper and 1 mm. aluminum filtration. The tumor dose was 4,100 r. The patient tolerated the second series of treatment without nausea or vomiting and lost



Fig. 4. Case 2. Mrs. Charles G. 10 months after X-ray treatment.

no weight. Fig. 6 shows the skin reaction at its height two weeks after treatment. This healed without difficulty in four weeks. The patient is symptom-free now for one year and four months since the first treatment and seven months since the second series of treatment. Fig. 7 shows the stomach at the present time."

I had just read the article and case reports by Dr. Merrit when I was called upon by one of my colleagues to try and do something for a patient of his dying with gastric carcinoma. This was in 1936. The palliative results were striking. The history of this case is as follows:

Mr. Fred L., age 60, first seen on June 29, 1936. This patient gives a history of having gotten very hot while working in the field one year previously and then drinking a large quantity of cold water. During the night following this he had a severe hemorrhage from the stomach of bright blood. He was kept in bed for five weeks and at this time (June, 1936)—one year later—he has a severe secondary anemia, hemoglobin 60%, erythrocytes 3,500,000. There is a marked loss of weight, probably 30 to 40 pounds. On physical examination there is tenderness and rigidity in the upper part of the abdomen, particularly to the left of the midline. There is some relief from pain on the taking of food.

Fluoroscopic examination: The stomach is long and narrow, fishhook in type and fills promptly. The peristalsis is hyperactive and on close examination there is an irregularity, constant in character, involving the pylorus. The stomach on the whole is dilated.

He was subjected to a series of 30 X-ray treatments, 300 r a day, with a total of 3000 r over each of three fields, anterior, lateral and posterior over the upper abdomen with the following factors: 200 k.v. (peak), 10 ma., 50 cm. distance, 4 mm. copper filter. These treatments were given between July 8, 1936, and August 12, 1936. During the course of treatment he lost ten pounds in weight and by the end of the course of treatment he began to improve quite markedly and where he had been able to scarcely eat anything because of pain, by the 29th of August, 1936, he was eating anything and everything, and had no pain in the abdomen.

This continued and he went back to work firing a boiler in a laundry. He continued well, gaining in weight and strength for the next eight months when he had a return of his pain and loss of weight. In March, 1937, he was given a series of sixteen treatments over the upper abdomen, two fields right upper quadrant and left upper quadrant, a total of 2400 r over each field.

The pain was again relieved and his strength returned, but two months later he had a severe relapse, had to give up his work and finally died on the 24th of February, 1938—twenty months from the time he was first seen and thirty-two months from the time of his first gastric hemorrhage.

The palliative effects of the roentgen therapy in this advanced case were so striking and gratifying that I have since treated nine other cases. Two of these are, two years after treatment, apparently well and working every day. I will cite one of these cases:

Mrs. Charles G., aged 65, was admitted on September 29, 1936. She states that during the past year there had been a gradual loss of weight with a total loss of weight of fifty pounds. She complains of a dull aching pain through the upper abdomen, most severe in the epigastrium. This pain begins about one hour after eating and lasts until the next meal. When her stomach is empty and she has pain, the taking of food will relieve it temporarily. On fluoroscopic examination following the administration of barium meal the stomach filled readily, was in good position and good tone with active peristalsis. The outlines of the greater and lesser curvature were clearly seen but there was a regular, crescentic, persistent inden-

tation on the greater curvature in the mid-portion. This indentation showed a lack of peristalsis.

A series of four radiographs of the stomach were made and this irregularity on the greater curvature was found to be persistent. The pylorus and duodenum were smooth and regular in outline. On the basis of the persistent filling defect on the greater curvature, together with clinical symptoms, a diagnosis of carcinoma of the stomach was made.

She was treated by a series of thirty treatments, 300 r each, over three fields in the upper left abdomen anteriorly, laterally and posteriorly, 3000 r units being administered to each field. The fields were 20 x 20 cm. square and the following technical factors were used: 200 kv. (peak), 60 cm. distance, 8 ma., Thoraeus filter with equivalent of 2 mm. copper.

Three weeks following the treatment she had a very definite skin reaction with blistering, followed by tanning and desquamation.

She has been seen at regular intervals since; has gained forty-five pounds in weight; and does her own work and is apparently in excellent health. There has been no return of her gastric symptoms.

A radiograph was made on the 10th of June, 1937, 10 months after the first roentgen examination, which reveals only a slight crescent indentation of the greater curvature and peristalsis appeared normal.

DISCUSSION

Ten cases have been treated by this method and two of the ten are apparently well twenty months or more since treatment. I have, therefore, convinced myself that modern X-ray therapy in small doses over a prolonged period of time is of definite palliative value in carcinoma of the stomach. We know that gastro-enterostomy is of definite palliative value.

Therefore, we have at hand today, two effective methods for the palliation of advanced carcinoma of the stomach—gastro-enterostomy and high voltage prolonged X-ray therapy. Waters has proven that some adeno-carcinomas of the stomach, contrary to accepted opinion, are radio-sensitive.

Why not combine the two methods? Levin (1), it is true, has tried and discarded the X-ray method, but as Pohle (8) says, "There is no doubt in our mind that the 'how' of irradiation, the choice of the method and its technical application, is of the greatest importance; it partially determines the degree of success."

Pohle's statement cannot be over-emphasized—the technical application of the X-rays, the skill and experience of the roentgen therapist, are certainly just as important as the skill and experience of the surgeon in the use of scalpel and scissors.

Let me state definitely that roentgen therapy can show only a small percentage of success in the treatment of gastric carcinoma, but these few cases reported indicate what can be done and point the way. Much remains to be done, but I believe a first basic step has been made. By joint action between surgeons and roentgen therapists, further improvements can be made and more satisfactory results achieved.

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A Gastroscopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions*

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THE rapid progress which clinical gastroscopy has made in the past few years gives it a prominent place as a diagnostic procedure to determine gastric disease. This is especially evident in the study of gastritis. In Europe, numerous gastroscopic as well as histopathologic studies suggest that the disease is prevalent. In America, however, not as much investigation has been done to substantiate such findings. We therefore have selected for gastroscopic study, several groups of cases which commonly confront the physician with a gastric symptomatology which the ordinary diagnostic measures may not always explain. Since so little is known about the incidence of gastritis, we have attempted to contribute such a study from our series.

Among the clinicians who stimulated great interest in this type of study are Henning (1), Schindler (2) and Moutier (3). Besides these three outstanding investigators, there are a number of others who contributed to the gastroscopic study of gastritis, the most noteworthy probably are the reports of Gutzeit (4), Chevallier (5), Benedict (6), Swalm and his associates (7), Gaither and Borland (8) and others.

Although there are several good classifications of gastritis, we have adopted Schindler's simple classification. He divides his cases into acute and chronic forms. The type of cases we have observed were almost all chronic in nature and we therefore shall confine ourself to that group. Chronic gastritis is divided into superficial, hypertrophic and atrophic types. Inflammation of the stomach is characterized by the fact that the normal smooth glistening orange red appearance of the mucous membrane is changed.

In superficial gastritis, the stomach has the appearance of a definite inflammatory reaction taking place. The color is dusky red and the mucous membrane is dull in appearance. There are hyperemic areas and erosions of varying size and hemorrhagic spots may also be seen. Occasionally gray patches of tenacious adherent mucus are observed.

In hypertrophic gastritis, the outstanding impression that the observer gets is the marked increase in size of the rugae. In some cases, there does not appear to be any marked inflammatory reaction. However, the mucous membrane may appear thickened and swollen. The nodular formations which have been described frequently in the literature, we have only observed rarely. In some cases there is also a definite

inflammatory reaction, here, it becomes more difficult to distinguish it from superficial gastritis.

In atrophic gastritis, the mucous membrane appears thin and pinkish gray in color. The rugae are either effaced or markedly thinned out and in some cases a fine network of veins is observed.

We have also observed a type of gastritis which is limited in extent. It may be confined to the antrum of the stomach. This antral gastritis may be any of the three varieties mentioned. Another type of gastritis that is frequently seen is in gastro-enterostomized stomachs. Here the inflammation is usually peristomal in extent and may be severe in inflammatory reaction. This reaction in the stomach has been observed in patients even several years after their operation.

It is important to consider that the present day conception is that the majority of digestive disorders are not the result of definite gastric or duodenal organic disease. Such disorders are usually termed "dyspepsias" and are classified as organic, reflex, systemic and functional. Blackford (9), Foster (10), Davis and Van der Hoof (11) and the more recent work of Rivers and Ferrerra (12), covering a total of 11,523 cases, agree that the organic group comprises only from 11.2 to 14% and the functional group as high as 22 to 25%; the remainder being due to reflex and systemic causes. If we exclude the organic group, we find there is usually great difficulty in making a positive diagnosis. This is strikingly evident in the functional group of cases. The tendency is to make such a diagnosis by an eliminative process and consequently to include erroneously those conditions which usually cannot be diagnosed by the ordinary means available.

Gastritis is the outstanding gastric condition which is commonly mis-diagnosed. That it is much more common than is generally realized is shown by the fact that quite a large number of such cases were found by gastroscopic study, to be included among the so-called "gastric neuroses," and also were found to be associated with other gastric pathological conditions.

In a series of sixty-two cases, both clinical and X-ray studies failed to explain epigastric symptoms. A diagnosis of functional dyspepsia was made. Gastroscopic study revealed no lesions in twenty-five cases, twenty-one had a chronic gastritis, three had peptic ulcers (on the posterior wall of the stomach), two had small polyps, six had pylorospasm and in five the examination was unsatisfactory. It is interesting to note that 46.8% of these had definite organic gastric disease. In a series of this type, where both clinical and roentgen study failed to make a diagnosis of organic

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disease, it is very striking to find the incidence of organic gastric disease to be so high. Even though this series is small, we may conclude from it that lesions on the posterior wall of the stomach, may at times, not be diagnosed by routine clinical study. That gastritis is quite common among the so-called functional dyspepsias becomes quite evident when we consider the fact that in this series, the incidence of gastritis is as high as 37.8%.

A group of gastro-enterostomized patients was studied. These patients all gave a history of having the operation performed for the relief of peptic ulcers. In the majority of these cases, several years had elapsed since their operation. Twelve such patients were gastroscopied. They all gave a clinical impression of a possible gastrojejunal ulcer in spite of negative X-ray findings. In six, no abnormal findings were noted; in five, a chronic gastritis of the peristomal type was observed and in one case, the examination proved unsatisfactory. It must be stressed that in this series, although the incidence of gastritis is impressive, it is not as high as that recorded by Gaither and Borland (8) who found "active and severe inflammatory changes in fourteen out of fifteen such cases—even two years after operation."

We also selected a number of duodenal ulcer patients whose symptoms persisted in spite of adequate ulcer therapy. These were the cases which failed to respond to adequate form of therapy, previously reported in the *A. M. A. Journal* (13). Sixteen such patients were studied. These patients were gastroscopied to determine if possible the reason for their resistance to therapy. In eight, no abnormal findings were noted in the stomach; however, in a corresponding number of patients, a quite extensive gastritis was observed. In the remaining two, a fixed pylorus due to cicatrization was seen. It must also be borne in mind that an associated duodenitis may also have existed. This of course cannot be ascertained gastroscopically. With such findings, one is strongly influenced to believe that the associated gastritis or possible duodenitis may explain to a great extent why certain types of duodenal ulcers will not readily respond to adequate therapy.

Another interesting series of cases that we studied for their possible relationship to gastritis were the definitely diagnosed gastric malignancies. In the majority of these cases, biopsy specimens were obtained either at laparotomy or at autopsy to confirm the diagnosis of malignant disease. Twenty-seven such patients were gastroscopied. In ten, the gastric mucosa not involved by tumor was normal. However, in thirteen, gastritis was observed. Of these, nine were of the atrophic variety; three, superficial, and one of the hypertrophic type of gastritis. In the remaining four, examination was unsatisfactory. In this series, the percentage of associated gastritis is higher than that of any other group we had studied. The role that gastritis, especially of the atrophic type plays in the etiology of carcinoma of the stomach is problematic. However, with such a high incidence of gastritis, it probably is an important factor in the symptomatology of these cases.

Still another interesting group of cases studied were the patients having true achylia. In our study of sixteen such cases, as many as twelve of these had definite atrophic gastritis; three were of the hyper-

trophic type; and in one, the gastric mucosa appeared normal. It will be seen that although as high as 94% in this series had gastritis, only 75% were of the atrophic type.

The general clinical conception that true achylia is associated with atrophy of the gastric mucosa is being seriously questioned by gastroscopic studies. Henning and Jurgens (14) reported a study of twenty-nine patients demonstrating achlorhydria after histamine injection and found atrophy of the mucosa in four and severe gastritis in thirteen instances. A. Bonadies (15) also reported a gastroscopic study of sixteen cases of achylia. He stated that he observed only seven cases of "typical gastritis," two showing atrophic changes and in the remaining six, no abnormal changes were noted in the gastric mucosa. However, it is not definite that his series were all histamine achlorhydria cases. Gaither and Borland (8) in their recent report also stressed that they have seen "atrophy with achylia, achylia without atrophy and atrophy with normal gastric juice." A still more recent gastroscopic study made by K. Luhr and M. Gulzow (16) in pernicious anemia patients indicate that even in this type of case, they discovered acute and chronic gastritis and they conclude that "pure atrophy of the non-inflammatory type" is not always characteristic of pernicious anemia. The conception is that some form of gastritis usually is present with achylia and it is not necessarily of the atrophic type. Our findings support such a contention.

In a number of instances, the gastroscopic examination proved to be unsatisfactory. In the majority of these patients, despite the fact the stomach was properly emptied, the secretion was so excessive that it rapidly flooded the field and it was impossible to make an accurate diagnosis. This type of phenomenon was considered as pathological and a diagnosis of "succorhea" was made. In a few cases because of excessive secretion of mucus, the stomach was not properly emptied and poor vision of the gastric mucosa resulted. Also in an occasional instance, the patient resisted the passage of the instrument and the examination had to be abandoned.

In analyzing our findings, it will be seen that the incidence of gastritis is highest in the true achylia cases, being 94% (only 75% being of the atrophic type). The gastritides associated with gastric carcinoma follow with 59.8%; those associated with chronic resistant duodenal ulcer 50%; those associated with gastro-enterostomies 45.5%, and those found in the undiagnosed group (functional dyspepsias) follow with 37.8%. The most impressive finding is that in the five groups studied more than one-half (54.5%) of all the cases examined had some form of gastritis and these were only diagnosed by gastroscopic study.

Such findings would tend to support the contention that gastritis is quite as prevalent in the United States as in Europe. Our findings are further substantiated by the fact that Swalm, Jackson and Morrison (7) in a gastroscopic study have found that the incidence of gastritis was approximately just as high in their series of 135 cases. In referring to the incidence of gastritis, they also quote R. Schindler, who has done a great number of gastroscopies abroad as well as in this country, as stating that "his statistics are identically the same in Chicago and the middle west as in Germany" and in a recent publication, Schindler and

his associates (17) state that in a series of 2,500 cases, the incidence of gastritis is about 50%.

In attempting to classify the incidence of the types of gastritis, difficulty was encountered in some cases. At times it was difficult to distinguish between superficial and hypertrophic types of gastritis and occasionally various degrees of the two or even the three types were noted in the same patient. In such cases, the predominating lesion was given the preference. Another factor that should play an important role in the classification of gastritis is the degree of disease observed. We noted marked variations or different stages of the same type of gastritis. In the atrophic type, the degree of atrophy varied, from the moderate thinning of the rugae to their complete effacement and thinning of the mucous membrane with arborization of vessels. It is difficult to conceive of atrophic gastritis as a definite type, with one characteristic gastroscopic picture. It is more logical to accept Moutier's version of it as progressive disease. We have observed that often various stages of atrophy may be found in the same patient. Superficial gastritis varied from mild inflammation of the mucous membrane to a marked inflammatory reaction, showing an angry looking mucous membrane, with superficial erosions and occasional hemorrhage or exudate. The hypertrophic type varied from a moderate increase in the size of the rugae to a marked cordlike thickening giving one the impression of mucosal edema. Still another factor to consider is the extent of involvement. In some cases, at times it was antral in extent, and in a good many of the gastro-enterostomized patients, it was only peristomal. However, in determining the incidence of the types of gastritis, its classification had to be simplified.

A group of six cases which is not included in the above series was also studied. These were patients in whom the diagnosis of hypertrophic gastritis was made by roentgen examination. Clinically, these patients presented an unexplained epigastric symptomatology. Gastroscopic diagnosis agreed with the X-ray evidence. However, it should be stressed that they all had an advanced type of hypertrophic gastritis. It will be seen that the frequency of gastritis diagnosed by X-ray study is comparatively very small.

Occasionally a clinical and X-ray impression of a gastric cancer may turn out to be a form of gastritis. We observed two such cases, both diagnosed as gastric cancer. In one case, gastroscopic study ruled out a neoplasm and saved the patient from surgical inter-

vention. In the other case, however, even the gastroscopic picture resembled carcinoma so much that exploratory laparotomy with biopsy study had to be performed to rule out carcinoma.

CONCLUSIONS AND SUMMARY

1. A series of 143 patients on whom more than 200 gastroscopic examinations were done is reported. It is found that the diagnosis of gastritis is difficult to make. Clinically it does not adhere to any definite syndrome. Clinical, laboratory and roentgen study does not give very much information in the majority of instances except in an occasional case of advanced hypertrophic gastritis where the X-ray may make such a diagnosis. Pathologic verification of such conditions is greatly handicapped because at post-mortem, extremely rapid autolysis of gastric tissue takes place.

2. When clinical and X-ray study fail to explain gastric symptomatology, there is a strong tendency to relegate the patient to the so-called "functional dyspepsia group." That gastritis is much more common among such patients than is generally realized is greatly emphasized by the fact that a surprisingly large number of such people (37.8%) had a definite chronic gastritis.

3. The general clinical belief that true achylia is an expression of atrophy of the gastric mucosa, is not supported by gastroscopic study. The gastroscopic conception is that where there is true achylia, there is usually gastritis present, but it is not necessarily of the atrophic type.

4. Gastritis may play an important role in patients who have peptic ulcers, neoplasms, and gastro-enterostomies. Such an association of gastritis may not only influence the symptomatology presented by the patient, but may also explain why some cases do not readily respond to therapy. In the series we studied, the incidence of associated gastritis was exceptionally high.

5. The most striking finding in this study is that more than one-half (54.5%) of the five main groups studied had some form of gastritis and it was only by gastroscopy that such a diagnosis was made. Such finding would tend to make gastritis a common rather than an occasional gastric disease.

6. It must also be stressed that gastritis may occasionally simulate a gastric neoplasm to such an extent that even gastroscopically, it may be difficult to differentiate between the two.

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Studies in Human Biliary Physiology*

1. Fasting Rate and Quantity of Bile Secretion

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CONSIDERABLE controversy exists today on the quantity and rate of secretion of bile in normal human beings. While an extensive bibliography has accumulated on biliary secretion in experimental animals, the literature on secretion in humans is comparatively sparse, and is of necessity limited to observations made on patients with natural or surgery-resultant fistulae. Such observations are subject to many criticisms, and rightly so. The search for reliable data must of necessity be limited to those humans who comply with the following requirements:

1. The fistula must be complete so that all the bile secreted by the liver can be collected. The passage of however slight a quantity into the intestinal tract will invalidate any determinations.

2. The gall bladder must have been previously removed. The concentrating power of this organ will materially interfere with the volumetric output of the liver. It will further negate the value of any data on choleresis, since its cholagogue action is very important.

3. The liver of the subject studied must be apparently normal. Hepatic disease is quite apt to interfere with bile secretion.

4. The collection of the bile must be complete. Any leakage around the fistula will destroy the importance of any conclusions.

The widely divergent reports in the literature are due to either failure or inability to observe these criteria. Table I indicates the extent of this range of opinion.

More recently, Koster, Shapiro and Lerner (2) have found the daily volume to range between 420 and 500 cc. in a cholecystectomized female with a T-tube fistula.

A short time ago, there was admitted to our surgical service, a patient with a total external biliary fistula which met all the requirements previously enumerated. A brief description of this patient follows:

Mrs. E. M., white, aged 25, weight 45.5 kgms., in good general condition. The patient had had a cholecystectomy done at another institution after a diagnosis of cholecystitis with cholelithiasis had been made. She was fairly well for a short time, but soon noticed a progressively increasing jaundice accompanied by clay-colored stools and diarrhea. An exploratory laparotomy revealed a complete stenosis of the distal portion of the supra-duodenal segment of the common duct. No calculi were found, but the common and hepatic ducts were dilated above the stenotic segment. This portion was cut through and could not be probed through into the duodenum due to complete fibrosis. It is highly possible that this pathology was the

result of some accidental injury to the common duct during the first operation. An attempt to bridge across the common duct and duodenum with a T-tube was unsuccessful, because at no time after the second operation was any bile found in the intestinal tract. After the removal of the T-tube, all the bile secreted was collected from the abdominal fistula opening. Hippuran injection

TABLE I

Amount of biliary secretion in man (Sobotka) (1)

Year	Author	Daily Amount of Bile	Remarks (Body-Weight)
1733	Amyand, Stuart	650 ml.	Perforated abscess of gall bladder
1764	Haller	720 ml.	Estimate
1817	Douglas	850 ml.	Estimate, analogy to dog
1835	Monro quoted in Todd	350 ml.	Pulmonary fistula
1864	Bischoff and Lossen	11 to 34 gms. total solids	
1866	Harley	600 ml.	Echinococcus fistula
1867	Robin	500 ml.	Quoted by Pfaff and Balch
1871	Ranke	625 ml.	Echinococcus fistula (47 kgms.)
1872	von Wittich	532 ml.	Fistula
1873	Westphalen	453-556 ml.	Bronchial fistula
1884	Yeo and Herroun	354 ml.	Fistula, cancer, 50 kgms.
1885	Murchison	<900 ml.	Estimate
1889	Copeman and Winston	780 ml.	Fistula stone operation (75 kgms.)
1890	Robson	850 ml.	Fistula stone operation (53 kgms.)
1891	Paton and Balfour	518-814 ml.	Surgical fistula (73 kgms.)
1897	Pfaff and Balch	450-550 ml.	Surgical fistula (51 kgms.)
1899	Zeynek	300-400 ml.	Fistula stone operation (80 kgms.)
1902	Brand	500-1100 ml.	Nine surgical cases
1904	Levene et al	460-860 ml.	Surgical fistula
1909	von Rzentkowski	360-870 ml.	Fistula of hepatic duct
1910	Bacmeister	100-340 ml.	Four surgical cases
1916	Cosentino	300 ml.	
1921	Nelson and Meyer	885 ml.	
1922	Harer et al	800-1200 ml.	Estimate
1923	Gundermann	250 ml.	Hunger value

*From the Department of Surgery and Pathology, Beth-El Hospital, Brooklyn, N. Y.
Submitted November 25, 1938.



Fig. 1. Hippuran visualization of biliary fistula tract and common and hepatic ducts proximal to obstruction. Note absence of dye in distal portion of common duct and duodenum.

into the fistulous tract showed the common duct ramifying into the larger ducts of the liver, but no evidence of any dye could be found in the duodenum or the duct leading to it (Fig. 1). After a stormy convalescence, the patient was discharged, having been taught to collect her own bile and drink it with each meal. On her present admission to the hospital, the various liver function tests were done to determine the apparent efficiency of her liver. The various blood tests, blood chemistry values and liver function tests, as well as microscopic analysis of the collected bile were all found to be normal. The results of these tests are as follows:

Hemoglobin 85% (Sahli), R.B.C. 4,200,000, W.B.C. 8,200. Differential—Polys 67%, small lymphocytes 23%, large lymphocytes 5%, eosinophils 3%, basophils 2%. Blood chemistry—Urea 12 mgs., Creatinine 1.5 mgs., uric acid 3.0 mgs., Glucose 85 mgs., Albumin 5.2 mgs., Globulin 2.2 mgs., Fibrinogen 0.5 mgs., Cholesterol 180 mgs., Cholesterol ester 100 mgs., Bilirubin 0.2 mgs., Icteric index 4. Bleeding time 3 minutes, Coagulation time 5 minutes. Galactose tolerance test 1.5 gms., Hippuric acid test 2.82 gms. Blood Wassermann negative.

The patient was therefore judged to be a fit subject for studies on bile secretion in the normal human.

Procedure: The abdominal fistula opening was intubated with a tightly fitting catheter which was further sealed off with collodion and adhesive strips to make it leak-proof and pull-proof. This catheter was then connected through a glass connecting tube with a length of rubber tubing sufficient to prevent any kinking and pull on the catheter. The end of this tubing was inserted into cotton-stoppered test tubes which were changed hourly. The patient was then put on a gradually diminishing diet

TABLE II

Hourly volumetric output—no food, no bile, varying quantities of water (100-500 cc.), with and without suction

Time P. M.	Volume in cc.		Time A. M.	Volume in cc.	
	Suction	No Suction		Suction	No Suction
12-1	20.0	19.7	12-1	17.0	15.2
1-2	22.0	21.8	1-2	16.0	13.8
2-3	24.0	21.3	2-3	15.0	14.0
3-4	24.0	18.0	3-4	16.0	15.0
4-5	20.0	23.6	4-5	18.0	17.0
5-6	21.0	17.5	5-6	19.0	20.0
6-7	20.0	21.0	6-7	19.0	18.8
7-8	20.0	22.9	7-8	20.0	20.6
8-9	20.0	18.2	8-9	26.0	25.0
9-10	22.0	19.2	9-10	23.0	22.3
10-11	17.0	23.3	10-11	24.0	25.0
11-12	16.0	16.0	11-12	22.0	19.0
Total volume in 24 hours without suction.....468.1 cc.					
Total volume in 24 hours with suction.....480.0 cc.					

These values are graphically illustrated in Fig. 2.

with a constant fluid intake until she became accustomed to starvation without discomfort. She was then deprived totally of food on three different test days, with intervening days during which a normal diet was administered. This diet was then again reduced gradually, so that on the day before the next test day (when she was again totally deprived of food) her food intake was negligible. Her water intake remained constant. During these starving test days, varying quantities of water were allowed the patient. None of the collected bile was re-administered to the patient. The bile was collected hourly, day and night, for 24 hours during these starvation test periods.

Koeour and Ivy (3) have suggested that variations in hourly output of bile during the day and night found by previous investigators might be due to temporary and partial blockage of the fistulous opening. Collecting their specimens with the constant application of suction, they could find no variation. We therefore repeated our experiment using moderate constant suction applied to the catheter intubated into the abdominal fistulous opening. The remainder of the procedure during this collection was exactly the same as it had previously been without the

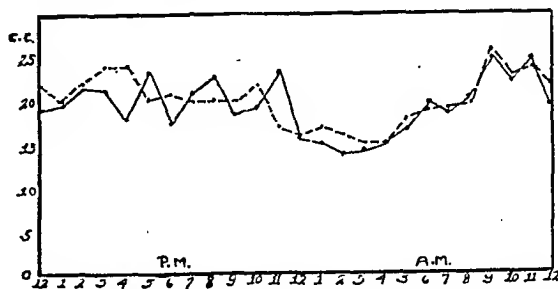


Fig. 2. Graphic representation of hourly bile secretion under basic conditions (see Table II). Note the general absence of variations except for consistent diminution during the hours from 11 p. m. to 5 a. m. without the use of suction (solid line), and from 10 p. m. to 4 a. m. with the use of suction (broken line).

application of the suction, with the exception that the bile was collected in a cylinder graduated in cubic centimeters. A representative and typical chart of hourly values utilizing both methods of collection is presented in Table II.

It will be noted that no significant differences exist in the hourly secretion with or without the application of suction. Similarly, in both cases there was a distinct diminution in the quantity of bile collected during a 6 hour period of the night and early morning, the decrease being approximately the same with and without the use of suction. Our patient, in bed throughout these experiments, was actually asleep and at basal metabolic levels during the night, a condition probably difficult or impossible to attain in an experimental dog. This may explain the difference in our results from those of Kocour and Ivy. Parenthetically, it should be noted that the patient herself had noticed that less bile flowed from the tract when she was quiet for several hours, and that the flow was increased by her activity.

SUMMARY

1. In a healthy patient, with an apparently normal liver and a total biliary fistula, observations were made on the rate and quantity of biliary secretion when the subject was starved and no bile was administered orally.

2. The hourly rate of flow during the day and night was found to be fairly regular.

3. There was, however, a 6 hour interval during the night and early morning, corresponding to the sleeping period, that showed an appreciable diminution of flow. This interval coincides with the period during which the subject's metabolic processes were at a minimum.

4. The administration of varying quantities of water had no effect on the rate of secretion.

5. The daily total output averaged between 468.1 cc. and 500.9 cc. or between 10.5 and 11.0 cc. per kilo of body weight. These values do not take into consideration the effects of intestinal bile as a secretory stimulant, bile having been excluded from the patient's economy during these studies.

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The Intravenous Feeding of Amino Acids

By

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INTRODUCTION

IN medical practice the feeding of human beings by other than oral means has long been recognized as a necessity under certain conditions. Up to the present certain salts and glucose have been the only materials injected. Patients decline fairly rapidly in the absence of tissue-building proteins.

Abderhalden (1) has established that proteins in the process of digestion are completely hydrolyzed. Moreover, Van Slyke (1) has shown by examining the blood before and during digestion, that it is in the form of amino acids that protein synthesis begins, since polypeptides when introduced into the blood stream are excreted unchanged.

It is not known in what proportion the various amino acids are absorbed by the tissues from the blood. Moreover, the present price of individual amino acids would prohibit their general use for such a purpose. In the experiments described below an inexpensive pure protein was hydrolyzed and the resulting mixture of amino acids utilized.

Considerable work has been done on feeding animals orally with mixtures of amino acids, but very little on their intravenous injection. Buglia (2) found by injecting hydrolyzed proteins that a considerable proportion of the amino acids was taken up by body and suggested that the animal could probably be fed that way.

Askroyd and Hopkins (3) have shown that if hydrolyzed casein is administered orally as the sole source of

protein, the animal loses weight and ultimately dies. But that if tryptophane, which is destroyed by acidhydrolysis, is added in small amounts to the hydrolyzate, normal growth is maintained. This seems to be due to the inability of the animal to synthesize the indol ring.

Casein was selected as the source of amino acids and hydrolyzed by means of sulphuric acid. Enzyme hydrolysis was not considered, since it would be difficult to separate enzymes completely before injection, while hydrolysis by bases racemizes the amino acids. Of the ten indispensable amino acids it has been shown that—tryptophane, histidine, phenylalanine and methionine can be replaced for growth purposes by their Antipodes. On the other hand, only the natural forms of valine, leucine, isoleucine, lysine and threonine are available for the use of the growing organism (4). Arginine has not yet been investigated.

EXPERIMENTAL

One litre of 15% sulphuric acid was used for each 100 grams of casein, and the mixture was digested on a sand bath under a reflux condenser for several hours after a portion withdrawn first gave a negative biuret test. The extra digestion was to ensure complete hydrolysis to amino acids. The mixture was then boiled with animal charcoal until colorless and filtered. Sufficient solid barium hydroxide to almost neutralize the sulphuric acid was added and the solution again filtered. The mixture was then diluted to two litres for each original 100 grams of casein, since it was

found that in a more concentrated solution the more insoluble amino acids such as tyrosine and leucine tended to precipitate out on standing. The mixture was adjusted to a pH of about 7.4 by means of sodium hydroxide solution. Then sufficient Ringer's salt to make the solution isotonic and about 10% glucose were added, and the pH was readjusted when necessary.

The solution was next filtered through a Seitz filter to sterilize it, although it was found to be just as efficient to autoclave the solution before adding the glucose, and then to add the glucose which had been sterilized in the dry form.

Rabbits were selected as experimental animals, each was fed approximately 80 cc. of the mixture as calculated on their energy and protein requirements, depending on their weights. At first the injections were made through a vein in the ear, but this method was found to consume too much time, so intra-peritoneal injections were carried out twice a day. The animals absorbed the food slowly from the peritoneal cavity. A few rabbits were run as controls, being fed the same amount of glucose solution without the amino acids. Fresh drinking water was always available. After each experiment the animals were sacrificed and the kidneys and liver as well as other internal organs were examined for signs of strain, but they appeared quite normal in each case.

The rabbits lost weight slowly after the first few days, although those that were fed amino acids as well as glucose lost more slowly than those which had only the glucose. It was then decided to add about 0.5 grams of tryptophane per litre of solution to the same mixture. Rabbits fed this diet were found to keep up weight fairly evenly for about a week, then to decline at a fairly steady rate. This loss may have been due to several causes: inadequacy of the protein mixture, to improper balance among the various amino acids, or to absence of other factors, such as Vitamin A. To test the latter supposition a Vitamin A concentrate, "Avalon," was obtained, and one drop was injected intravenously each day in addition to the regular intraperitoneal injections of the usual mixture plus tryptophane. This was found to lengthen the time before the animals lost weight. Probably other growth factors might be added advantageously.

In conclusion, rabbits fed intravenously or by intraperitoneal injections on a mixture of amino acids from hydrolyzed casein, supplemented with tryptophane and Vitamin A, lose practically no weight over a period of two weeks, and remain in normal physical condition.

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The Influence of Alkalis on Renal Function*

By

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THE clinical state of alkalosis and its association with impaired renal function has been widely recognized since the report of Hardt and Rivers (1). Cooke (2) points out three unanswered questions regarding the physiological effects of soluble alkalis: (1) Is there aggravation of pre-existing renal insufficiency? (2) Are the kidneys damaged by the alkalis? (3) Can these findings be attributed to extra-renal causes? Numerous observations have been made heretofore on the diminution of renal function when there is a marked change in the acid-base equilibrium toward the alkaline side, i.e., in uncompensated alkalosis (3, 4, 5, 6, 7). It is of interest that some such change in renal function may occur in apparently normal individuals when alkalis commonly used in the control of peptic ulcer are taken. There is available no adequate study on renal function variation in patients receiving poorly soluble alkalis and showing no signs of alkalosis.

Eighteen patients receiving a general diet while under observation in the hospital for minor ailments, were given 20 to 30 grains of a mixture of calcium carbonate and magnesium oxide (in the ratio of eight to one) every hour from 7 A. M. until 9 P. M. daily.

Before starting the alkalis, and again after the alkalis had been administered for a period of seven to eight days, the following observations were made by usual clinical laboratory methods: phenolsulphonphthalein excretion for periods of 15 minutes and two hours (intravenous administration of the dye); maximum urea clearance of Van Slyke (Koch's (8) methods for urea); early morning specific gravity readings on urine (neither food nor fluid for the preceding twelve hours); urine dilution (four-hour volume of urine after ingestion of 1500 cc. on an empty stomach); carbon dioxide combining power of blood plasma (9) and chlorides of the blood plasma (10).

The accompanying table presents the laboratory findings from two patients for illustration. A slight, but definite, diminution of renal function is indicated by the several procedures for its estimation.

In the entire group studied, the urea clearance figures show an increase in one patient, a decrease in the remaining 17 patients. In ten patients of the group, after one week of alkali medication, the clearance was lowered by 30% or more. The phenolsulphonphthalein excretion for the first fifteen minute period was unchanged in two patients, decreased 5% in ten patients, decreased 10% or more in six patients, and increased in no patient after a week on alkalis.

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Submitted January 4, 1939.

TABLE I

Patient	Morning Sp. Gr.	PSP 15 Min. %	Dilution 4 Hr. Vol. cc.	Urea Clearance %	Blood Urea Nitrogen	CO ₂ C. P. %	Plasma Chlorides mgm. %
G. P. (before alkalis)	1.020	25	2050	70	9.7	66	571
G. P. (after alkalis)	1.012	20	1225	40	9.7	64	584
A. R. (before alkalis)	1.022	30	1215	113	10.3	62	705
A. R. (after alkalis)	1.015	25	550	61	17.4	68	795

In all the patients the carbon dioxide combining power remained within normal limits, but showed a slight tendency to rise during alkali medication. During the period of observation, the values for plasma chlorides increased more than 50 mgm. in two patients, decreased more than 50 mgm. in two patients and was altered less than 50 mgm. in the remaining patients. Assuming the normal range of value for blood urea nitrogen to be 8 to 20 mgm., it was found that the urea nitrogen rose above normal limits in but one patient after the use of alkalis.

Thus there is evidence of depression of renal

function as measured one week after the routine use of calcium carbonate and magnesium oxide in doses similar to those frequently administered in the medical management of peptic ulcer. This phenomenon appears to be associated with no significant change in the acid-base equilibrium of the patients. No explanation is offered for the mechanism of this change. It is planned to continue these observations and to include determinations of plasma pH, hemoconcentration, and the influence of other poorly soluble antacids.

Note: This investigation has been made with the assistance of a grant from the Ella Sachs Plotz Foundation.

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A Method of Measuring Acidity and Protein Digestion Within the Human Stomach*

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THE literature is replete with articles on the interaction between hydrochloric acid, pepsin and protein. Such knowledge has been gained chiefly in the studies of gastric secretions in the course of animal experimentation and from analyses of aspirated human gastric contents. This information has been of value particularly in the treatment of peptic ulcer. By attempting to reduce the corrosive action of gastric juice with antacids healing of the ulcerated area is thought to be hastened. The results obtained from either complete or partial neutralization give ample testimony that neither method is entirely satisfactory.

It is a well known fact that acid values obtained

from aspirated material do not hold true for any one particular region of the stomach. It seemed worth while to study the pH of gastric contents in situ to see if it would differ from the pH of gastric contents removed by tube. The purpose of this paper is to introduce a simple method of measuring gastric acidity and protein digestion within the stomach. Such a method might be useful in a study of the therapeutic value of antacids.

Method. An electrometer using a glass electrode was chosen. This machine has a pH range of from 1 to 13 with a claimed accuracy within 0.05 pH. The electrode is shielded against stray electrical interference so that measurements can be made wherever desired. By reducing the size of the usual arrangement a gastric electrode was made. The body of this

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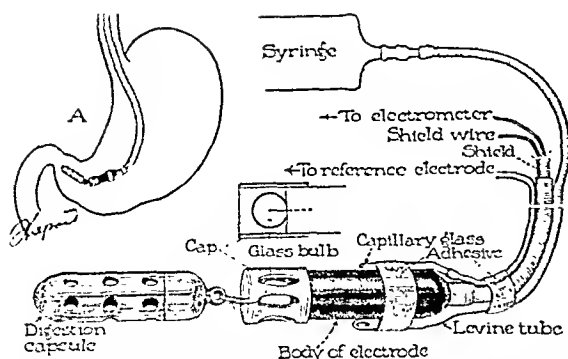


Fig. 1. Diagram of gastric electrode system with attached digestion capsule. A. Position of test elements in the stomach.

electrode (Fig. 1) is covered with hard rubber, is 2.75 cm. long and 1 cm. in diameter; at its distal end is the glass bulb 5 mm. in diameter, and at its proximal end the lead to the electrometer. This rubber covered shielded lead is 5 mm. in diameter and six feet long. A cap made of hard rubber protects the glass bulb. This cap is 1.5 cm. long and 1.2 cm. in diameter, has large longitudinal slits and an open end to allow circulation. Such protection prevents the glass bulb from touching the stomach wall and minimizes the chances of breakage. The liquid junction to the calomel reference electrode is accomplished by passing a saturated solution of potassium chloride through a small rubber tube fastened to the lead. This tube has a capillary

glass outlet attached to the body of the electrode with its opening 1 cm. above the glass bulb.

In order to compare pH values in situ with those of aspirated material a Levine tube with one opening was attached to the electrode system. The opening was made by an oblique cut 2 cm. above the glass bulb.

Digestion values were obtained by placing a cylinder of egg white in a metal digestion capsule. This capsule is 3.25 cm. long and 1 cm. in diameter, and has a screw cap, rounded ends and numerous holes. One end of the capsule was tied to the tip of the cap which protects the glass bulb of the gastric electrode. Under fluoroscopic control the electrode with its attached digestion capsule was placed in the antral region of the stomach (Fig. 1-A).

Egg white was prepared by boiling large fresh eggs for twenty-five minutes. Cylinders from the coagulated egg white were cut with a cork borer. In each test two cylinders from the same egg were chosen and weighed. One was put into the capsule and the other, as a control, into a glass of water at room temperature. Immediately after the capsule was withdrawn from the stomach, the remaining egg white was removed and gently washed to remove debris. Both cylinders were then put into separate vials and dried for twenty hours at 87° C. By comparing the fresh and dried weights a rough index of digestion was obtained. In some instances a chemical analysis for comparative changes between the control and experimental cylinders of egg white was made.

Two electrometers, calibrated at 39° C., and standardized on the same buffer solution were used in each experiment. The gastric electrode was attached to one

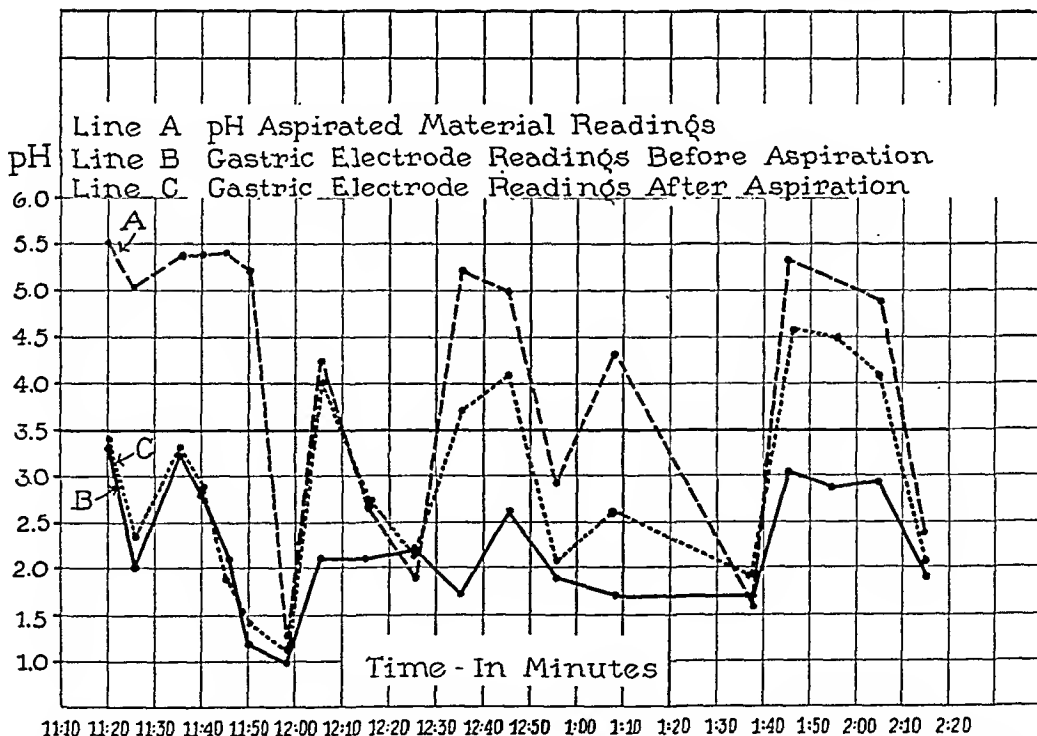


Chart 1. Patient F. C. pH curves obtained on routine ulcer management with three ounces of milk and cream mixture on the hour and fifteen grains of calcium carbonate on the half hour. Egg white showed marked digestion and a 20.8 per cent weight loss.

and the aspirated material tested with the second. A gastric electrode reading was made first. Following this, 20 cc. of gastric material was drawn back and forth through the tube three times and on the fourth withdrawal 8 cc. tested with the second machine and discarded. Often a second reading was then made with the gastric electrode to determine the effect produced by the aspiration mixing procedure. These manipulations usually consumed approximately three minutes. At the conclusion of each test both electrodes were again checked for accuracy and found to agree within 0.1 pH.

It seemed advisable to apply the Sippy neutralization method of ulcer management in our studies. All patients chosen had uncomplicated duodenal ulcer. These patients were given milk and cream every hour on the hour from 8:00 A. M. to 7:00 P. M. and powders every hour, on the half hour from 8:30 A. M. to 7:30 P. M., and then a powder every thirty minutes until 9:00 P. M. The usual tests for acid control were made by aspirations at 4:00 in the afternoon and 9:30 in the evening. Invariably, using Töpfer's reagent, these tests showed the acid to be under control. No medication or food except that described was given on the day of the test. The electrode with the digestion capsule was usually lowered into the stomach in the latter part of the morning and readings were taken over a three hour period without disturbing the position of the testing elements.

Results. The pH curves shown in the four charts are characteristic of a large number obtained when alkaline powders are used in the manner described.

The first three graphs illustrate the results obtained when different powders are used in the same individual; the fourth, using one of these powders on another patient, demonstrates the individual variation to the same amount of neutralizing substance. All charts show both prompt and delayed pH changes after taking an alkali. Such changes are most rapidly exhibited in aspirated material.

In Chart 1 wide variations in degree of acidity will be noted. No constant difference exists in values of aspirated material and those obtained with the gastric electrode. Aspirated material shows greater fluctuations and a higher average pH value than is found with the gastric electrode. The average for the latter is a value slightly above pH 2. At this level there was marked egg white digestion.

When the amount of alkali is increased, as is shown in Chart 2, average pH values increase for both determinations and fluctuations are not as great. For a short period it will be noted that values for aspirated material were somewhat lower than those from the gastric electrode. We find such an occurrence unusual. With this higher average pH only a small amount of egg white digestion occurred.

The curves shown in Chart 3 follow a course similar to those of Charts 1 and 2 although a different powder was used. The gastric electrode readings are comparable to those of Chart 1 and an equal amount of egg white digestion found.

Patient P. F. showed better neutralization on the same amount and type of antacid than patient F. C. This is illustrated by comparing Charts 3 and 4. The

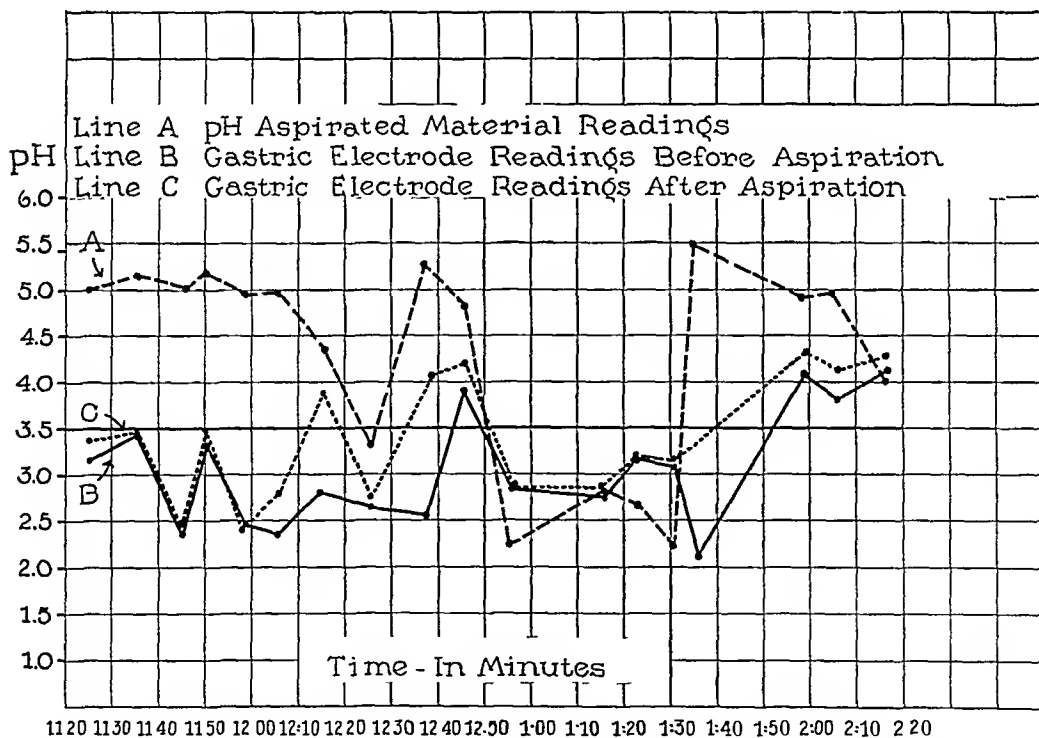


Chart 2. Patient F. C. pH curves obtained on routine ulcer management with three ounces of milk and cream mixture on the hour and twenty grains of calcium carbonate on the half hour. Egg white showed considerable digestion with an 11.1 per cent weight loss.

average gastric electrode reading is above pH 3.5 and no gross egg white digestion was seen.

DISCUSSION

It has been demonstrated by numerous investigators that the stomach does not function like a churn but rather as a hopper. Layers of food lie in strata with the cardia and fundus acting as the body and the pylorus as the mouth. The acid values are highest in the antrum near the pylorus. Since most ulcers occur in the first part of the duodenum and prepyloric area we are interested in neutralizing the stomach content in this region. In aspirated material as usually obtained it is difficult to evaluate the degree of acidity in the prepyloric region because of mixture with the more alkaline content from above. The acidity of the gastric contents when determined electrometrically from the electrode in the stomach and on the contents of the stomach removed in the usual manner, do not check, the intragastric electrode usually indicating a higher degree of acidity.

Gastric electrode readings were generally lower than those of aspirated material even though the opening of the aspirating tube was placed near the glass bulb. The volume of the highly acid antral content is small and no representative sample can be withdrawn. In the aspirated samples tested for comparison we must presume that there was considerable mixture with more alkaline material from other regions. Carbon dioxide loss during aspiration must be considered but this alone cannot explain the marked difference between the two readings.

In the process of aspiration there is considerable churning of the gastric content. To determine the effect of this procedure a gastric electrode reading

was often taken after aspiration. One would expect this second reading to give a value consistent with an average of the first reading and that of the aspirated material. This does not always occur. The shield about the glass bulb of the gastric electrode undoubtedly produces considerable lag because mucus and curds are inclined to adhere and prevent free circulation.

The motor activity, rate of secretion and volume of gastric content during a test period are not known. These factors undoubtedly play an important role in the results obtained. None of our patients had evidence of pyloric obstruction; therefore, a relatively normal emptying time was presumed. During periods of active peristalsis and small content, values obtained from the gastric electrode and aspirated material should be in close agreement. It is during the period of low motor activity that the greatest difference in values is expected. The pH of the aspirated material is usually promptly raised by the taking of an antacid while that shown by the gastric electrode is slower in exhibiting itself. Differences in rate of secretion probably occur but during the short interval between readings such variations are perhaps of minor significance. At times aspirated material has a lower pH than is indicated by the gastric electrode. The sensitivity of this electrode to rapid changes is undoubtedly reduced because of lag as previously stated. If this factor were removed the two readings should be in better agreement at such times.

The effect of various antacids in different doses has been studied. As would be expected, patient F. C. (Charts 1 and 2) shows better neutralization on twenty grains of calcium carbonate than on fifteen grains of the same powder. A powder containing

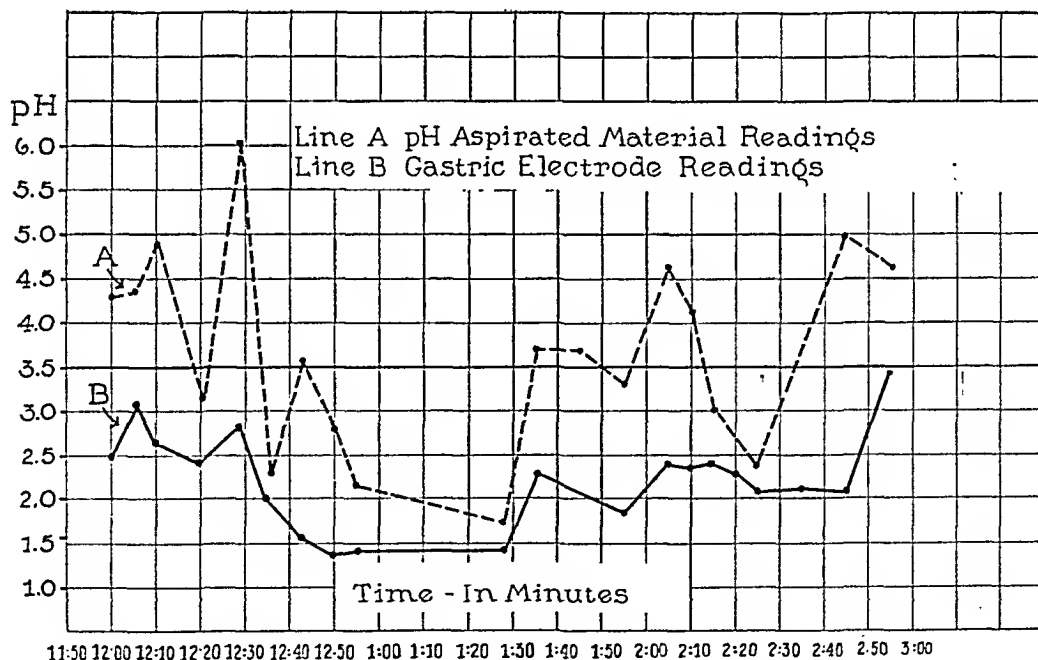


Chart 3. Patient F. C. pH curves obtained on routine ulcer management with three ounces of milk and cream mixture on the hour and twenty grains of tribasic calcium phosphate with fifteen grains of tribasic magnesium phosphate, on the half hour. Egg white showed marked digestion and a 23.2 per cent weight loss.

twenty grains of tribasic calcium phosphate and fifteen grains of tribasic magnesium phosphate seems as effective as the smaller dose of calcium carbonate in this patient. On the other hand, P. F. shows a much higher pH than does F. C. on the same powder. Since the amount of antacid is known in both cases we must assume that the amount of acid secreted was greater in F. C. than in P. F. Other antacids have been studied but space does not permit their discussion at this time.

Quantitative measurement of protein digestion is very complicated. In our studies it was found that the appearance of the test cylinder at the end of the experiment gave a good index of the presence or absence of peptic activity. It was hoped that weight loss would give a quantitative measure but when weight increases occurred and no visual digestion was present this method proved unreliable. Only in cases where evidence of active digestion could be seen was there a weight loss. Chemical analyses of test cylinders without gross digestion show that the calcium content is frequently doubled when calcium carbonate is given; when tribasic calcium and magnesium phosphate are given a tenfold increase in phosphate may occur. In these same samples nitrogen values are essentially unchanged. From this we must conclude that weight change gives an unreliable index of digestion because of adsorbed substances. At this time it is our impression that for practical purposes the appearance of the

egg white surfaces after a test gives sufficient information as to the presence of peptic activity.

In all charts shown it will be noted that line pH 3.5 is emphasized. Optimum activity for pepsin is placed between pH 2 and pH 3; above pH 5 it is said to disappear. Our studies indicate that little or no egg white digestion occurs when gastric electrode readings remain in the neighborhood of pH 3.5 or above.

CONCLUSIONS

1. A method of obtaining acid values in the antral region of the stomach is described.
2. A method of obtaining an index of protein digestion in the antrum of the stomach is described.
3. The pH of the antral content is lower than that of the stomach content as a whole.
4. No constant difference exists between the pH of antral content and that obtained by aspiration.
5. Gastric electrode pH values are usually lower than those of aspirated material.
6. Antral pH readings give a better index of local protein digestion than those of aspirated material.
7. Patients on a supposedly accurate neutralization therapy show active digestion of egg white in the antral region.

The electrometer and electrodes used in these experiments were made by the Coleman Electric Company, Maywood, Ill.

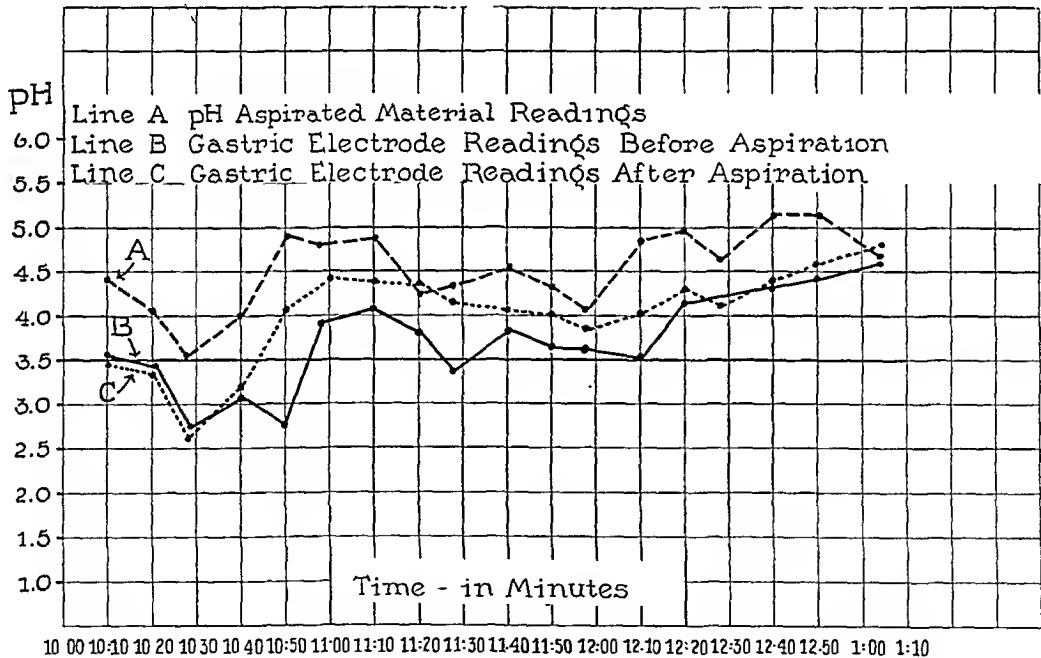


Chart 4. Patient P. F. pH curves obtained on routine ulcer management with three ounces of milk and cream mixture on the hour and twenty grains of tribasic calcium phosphate with fifteen grains tribasic magnesium phosphate, on the half hour. Egg white showed no digestion and an 11.9 per cent weight gain.

Phenolphthalein as a Test in Gastro-Intestinal Disease

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IN the study of gastro-intestinal disease there is a definite need for a rapid, simple, and accurate test that would determine the presence or absence of an organic lesion. Such a test would be of value: (1) in the differentiation between functional and organic disturbances with a saving of time, expense and discomfort of varied laboratory procedures; (2) in cases in which the patient is too ill for extensive studies or when such studies are inconclusive; and (3) for evaluating progress in ulcerative lesions of the gastro-intestinal tract under treatment.

A test which seems to fulfill such a need was reported recently by Woldman (1). He used a 1% solution of phenolphthalein in alcohol by mouth, testing the urine at two, four and six hour intervals for the presence of free phenolphthalein. Free phenolphthalein was found in the urine of 34 of 35 patients with gastro-intestinal lesions, while 75 of 77 subjects stated to be free of such lesions excreted none. Since Vamossy (2) states that the greatest portion of ingested phenolphthalein is excreted unchanged in the feces with the remainder being excreted in conjugated form in the urine, Woldman concludes that the presence of free phenolphthalein in the urine is evidence that there is some break in the continuity of the mucosa of the gastro-intestinal tract. Fantus and Dyniewicz (3) gave a thousand doses of phenolphthalein in capsules to students and ward patients, finding free phenolphthalein in the urines of 8.5% of the students and 1.5% of the ward patients. They found that the quantity of free phenolphthalein in the urine is dependent on the size of the dose and the interval between the voiding of the urine and its examination. Woldman tested the urine within a few minutes after it was voided to obviate the possibility of conjugated phenolphthalein being converted to the free form upon exposure to air. He gave only 0.1 gram of white phenolphthalein, in solution rather than in solid form, and he believes that the small dosage and administration in dissolved form is responsible for the value of the test.

An attempt was made to evaluate this test by applying it to 137 patients in the wards of the Philadelphia General Hospital. The patient was given 10 cc. of a 1% alcoholic solution of phenolphthalein by mouth while in a fasting state. The urine was tested immediately after voiding at two and four hour intervals, the test consisting of alkalization with several drops of 10% sodium hydroxide. The sixth hour specimen was also tested when two and four hour urines gave a negative result. Urine containing free

phenolphthalein turned a definite pink or red color upon the addition of one to three drops of sodium hydroxide, while urine without free phenolphthalein did not change in color.

In this series there were 21 cases proven by X-ray, operation, or autopsy to have lesions of the gastro-intestinal tract, and two cases in which the existence of such lesions were strongly supported by the clinical history. In the remaining 114 cases evidence was preponderantly against the presence of gastro-intestinal lesions. The results of the test are tabulated in Tables I and II, and reveal an accuracy of 56% in the gastro-intestinal cases, and 79% in the remaining cases.

These 137 cases include 69 cases in which the status of the gastro-intestinal tract was investigated, mainly by X-ray, but also by gastroscopy, operation, and autopsy. The test gave a correct result in 50 of these

TABLE I
Cases with gastro-intestinal lesions proven by X-ray and other studies

Diagnosis	Cases	Positive	Negative
Duodenal ulcer	8	3	5
Gastric ulcer	3	2	1
Carcinoma of stomach	10	6	4
Hematemesis	2	2	0
Totals	23	13	10

cases, an accuracy of 72%. In sixty-eight cases of the series no other gastro-intestinal studies were made, as they were not believed to be indicated by the physician in charge. The phenolphthalein test gave a negative result in 52 of these cases, an accuracy of 77%, if these cases can be regarded as having no gastro-intestinal lesion.

An analysis of Tables I and II reveals a higher percentage of correct results in the absence of disease of the gastro-intestinal tract. We believe this difference is due to the inclusion in Table II of ten cases classified as healed gastro-intestinal disease, and six cases classified as functional gastro-intestinal disease. The phenolphthalein test was negative in these sixteen cases, but because of the fallibility of clinical and X-ray diagnoses, it remains possible that unrecognized lesions of the gastro-intestinal tract were included in this group.

There were five negative results in eight cases of duodenal ulcer (Table I). These cases were reviewed

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Submitted February 20, 1935.

from the clinical standpoint, and it was thought that they should be included under the active gastro-intestinal lesion group, rather than as healed lesions. One case of active gastric ulcer failed to reveal free phenolphthalein in the urine. This patient was admitted with gross hematemesis, and X-ray study and gastroscopic examinations revealed a large gastric ulcer which responded to conservative treatment. Four negative results were obtained in ten cases of gastric carcinoma, although the lesions were later proven to be extensive. Two cases of hematemesis gave a positive result, although X-ray studies were negative. They both responded to the usual ulcer regimen of diet, alkalization, sedation, and rest, and the positive re-

lesions in any portion of the stomach or intestines.

From our results we believe that this test has definite limitations. That this was due to faulty application of the technique seems unlikely. There are many unknown factors which could influence the result of the test. The dose of phenolphthalein may have to be varied in individual cases. Little is known of the metabolism and excretion of phenolphthalein. It is possible that gastro-intestinal lesions might be coated by intestinal secretions, preventing absorption through a lesion of the mucous membrane. Gastric motility may have an effect on such absorption. The limitations of roentgenological examination may have influenced our results by the diagnosis of healed lesions as ulcerative.

Since this test is more often positive in cases with gastro-intestinal lesions, there is perhaps a relation to such lesions. However too little is known of the actual mode of absorption and excretion of phenolphthalein to draw definite conclusions as to its use in the diagnosis of gastro-intestinal disease. We believe that at present it can serve only as an adjunct to the history, physical findings, gastric analysis, X-ray study, and gastroscopic examination.

SUMMARY

(1) Phenolphthalein was given orally to 137 patients as a test for lesions of the gastro-intestinal tract.

(2) The test was correct in 56% of the cases with gastro-intestinal disease.

(3) The test was correct in 79% of the cases without evidence of gastro-intestinal disease.

(4) Of the 137 cases 69 had studies of various types to determine the status of the gastro-intestinal tract. The test was correct in 72% of these 69 cases.

(5) Cardio-vascular disease, infections, blood dyscrasias, and other conditions without obvious gastro-intestinal pathology gave a number of positives which impair the value of the test.

CONCLUSION

This test may be valuable as an adjunct in diagnosis, but more must be learned of the physiology involved before it can be considered reliable as a simple test for the determination of gastro-intestinal lesions.

We wish to express our appreciation to Drs. J. H. Clark and J. G. Reinhold for their cooperation and suggestions.

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TABLE II

Cases without proven gastro-intestinal lesions

Diagnosis	Cases	Positive	Negative
Healed gastro-intestinal lesions	10	0	10
Functional gastro-intestinal disease	6	0	6
Cardio-vascular disease	33	8	25
Pulmonary disease	12	3	9
Malignancy except of G.-I. tract	8	1	7
Liver disease	8	2	6
Blood dyscrasias	5	3	2
Subacute bacterial endocarditis	5	4	1
Skin disease	5	1	4
Arthritis	3	0	3
Miscellaneous	11	2	9
Undiagnosed	8	0	8
Totals	114	24	90

sult of the phenolphthalein test was considered as correct.

A number of incorrect results occurred in cases of heart disease (Table II). Minute hemorrhagic lesions with resulting breaks in the mucosa due to circulatory congestion might be postulated in these cases. One such case was admitted because of arteriosclerotic heart disease with auricular fibrillation. Her condition was not regarded as critical, and a phenolphthalein test was done with a strongly positive result. The patient died suddenly the next day at seven A. M., and an autopsy was performed three hours later. The entire gastro-intestinal tract was markedly distended, but grossly there were no hemorrhagic or ulcerative

The Histamine-Urine Test

Observations of the Secretion of Hydrochloric Acid and Urinary Hydrogen Ion Concentration on One Hundred Patients*

By

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NEARLY twenty years ago Leathes (1) suggested that the increasing alkalinity of the urine during the day might result from the change in the respiratory rate incident to the difference between the activity of subjects at night as compared to that of the waking hours. He furthermore intimated that in nephritic patient, the usual alkaline swing of the urine during the morning might not occur. Leathes (1) observations with regard to the effect of increased respiration were also confirmed by others (2, 3) but Fiske (4) and Campbell (5) presented data tending to show that the alkaline tide occurred regularly after

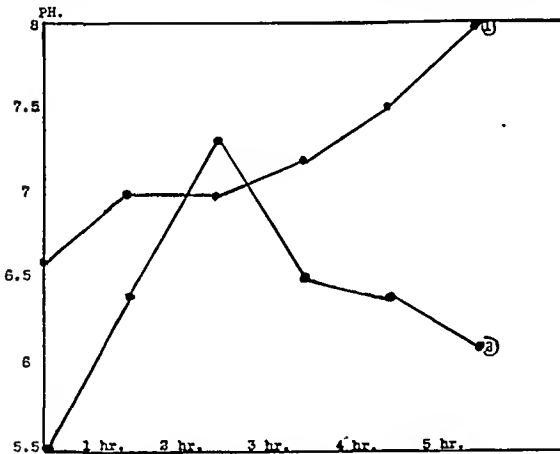


Chart 1. Examples of alkaline tides. 1 had arteriosclerosis. 2 had peptic ulcer.

meals, and could likely be attributed, in part at least, to the secretions of hydrochloric acid by the stomach. The observations of Hubbard and Munford (6, 7, 9, 11) served to support the presence of the alkaline tide and suggested its gastric source. Although Benedict (8) had seriously questioned the existence of the alkaline tide, the observations by Hubbard and Munford (6, 9), Hubbard, Munford and Allen (10) and Hubbard and Allen (12) again demonstrated the presence of the alkaline tide and its relationship to the secretion of hydrochloric acid by the stomach. In these latter experiments, it was shown that the presence or absence of an alkaline tide agreed with the results of fractional gastric analysis in about 80% of the cases studied and that when a tide was present,

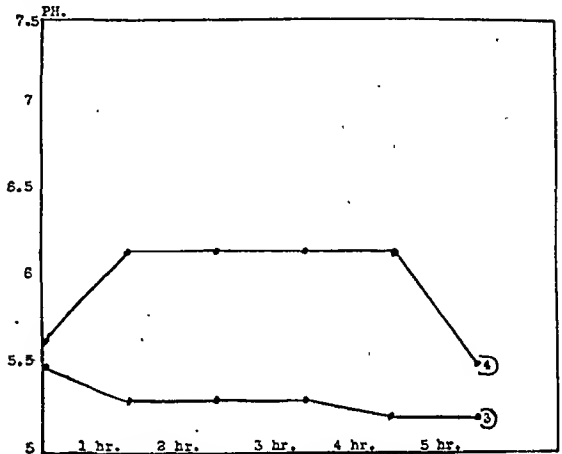


Chart 2. Flat curves. 3 had infection in G.U.

it seemed probable that the presence in the stomach of more HCl than is usually secreted in hypochlorhydria might be assumed. Later studies by Hubbard (14) suggested "that there are two factors which must be taken into consideration to explain changes in reaction of the morning urine. One is the secretion of hydrochloric acid by the stomach which causes the development of an alkalinity after a meal in bed. The other is, probably, an adjustment of the respiration to

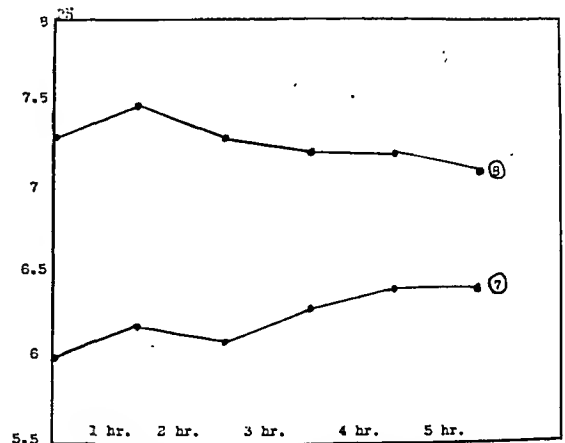


Chart 4. Typical flat curves. No alkaline tide. ⑦ A.L. and ⑧ G.T. had pernicious anemia. achylia.

*From the Medical Service of the University Hospital, Syracuse, N. Y. This study was aided by a grant from the Hendrick's Research Fund of Syracuse University Medical College.
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waking conditions which frequently shows its effect very early in the morning. If the interplay of these two factors is kept in mind, most results can be understood." A further point, suggested by Hubbard and Steele (15), indicated that in certain patients an increased alkalinity of the urine developed whether or not food was taken. Their interpretation of this occasional variation was that there was, in such instances, a "secretory rhythm" of the stomach, quite independent of immediate stimulation of the gastric glands by the ingestion of food. Also, there are some individuals, they (15) noted, in whom a marked alkalinity developed before any meal was eaten and which might persist throughout the entire morning period, even when food was omitted.

As a stimulant to gastric secretion, histamine has, in many instances, been preferred to the Ewald Test Meal and the dilute alcohol solutions. The present study was initiated in an effort to further confirm, or to refute, some of the previous observations with regard to the relationship between the secretion of HCl by the stomach and the alkaline tide in urine, the factor of food being thus eliminated. It was also hoped that we might check the validity of the statement (16) "it may be that a consideration of the urinary reaction will be found useful in establishing a possible gastric acidity when satisfactory analysis of stomach contents cannot be secured."

METHOD

Patients for study were given no medication the day before the test. At 9 P. M., the night before, the patients were asked to void and the specimen discarded. On awakening in the morning, the subject was asked to void—the specimen labeled "Fasting." He was then given 500 cc. of water by the mouth and 0.3 mg. of Histamine Phosphate subcutaneously. Urine specimens were collected at hourly intervals for the succeeding 5 hours and properly labeled. The urine specimens were collected in clean, dry urinals and the urine gently placed into clean, dry specimen bottles. ($\frac{1}{2}$ cc. of Toluol was added to the bottle). The specimen bottles were tightly corked, taken to the laboratory and examined for Ph, making a correction for the color of the urine in each case. Indicators used were Methyl Red, Brom-Thymol Blue and Phenol Red. Standards for comparison were the LaMotte sealed glass type, graduated in 0.2 Ph. Nearly all of the urinary specimens were examined for Ph within a few minutes after voiding but in exceptional cases the specimens were placed in an ice box until the determinations could be made. Patients were given no food or medication until after the completion of the tests and were kept at rest in bed until after the last urine specimen had been collected. Gastric analyses were made in the following manner: A Levin Tube was

TABLE I.

		ACHLORHYDRIC PATIENTS NO ALKALINE TIDE.									
NAME	DIAGNOSIS		PH URINE								
			Fasting	1hr.	2hr.	3hr.	4hr.				
Rivizzo #37826	Gastro-enteritis		6.3	6.1	6.0	5.8	5.7	5.5			
Lynch #28000	Pernicious anemia		8.0	6.2	6.1	6.3	6.4	6.4			
Stark #32409	Atrophic arthritis		6.4	6.6	6.7	6.7	6.7	6.6			
Lookwood #43701	C.N.S. Lesion— aortitis		5.6	5.7	5.5	5.6	5.6	5.5			
Wallace #40785	Hypertension		6.2	6.2	6.1	6.2	6.2	6.2			
Jones #36834	Chr. cholecystitis Cholelithiasis		6.0	6.0	6.0	5.6	5.6				
Jay #39846	Pernicious anemia		5.4	5.6	5.6	5.7	6.0	5.9			
Ailey #40810	Arterioscl. heart disease		5.2	5.5	5.4	5.3	5.2				
Everhart #39552	Chr. enteritis		5.7	5.5	5.7	5.6	5.5	5.7			
Clark #26170	Aortic aortitis Hypothyroidism		5.8	5.9	5.6	5.4	5.6				
Gates #37823	Chr. cholecystitis		6.7	7.0	6.9	7.7	7.5	7.0			
Cosco #10584	Pernicious anemia		5.1	5.5	6.0	5.6	6.7				
Farrieh #39247	Pernicious anemia		6.6	7.0	6.8	6.7	6.5				
Bastedo #37817	Tubo paresis		5.4	5.5	5.6	5.2	5.5	5.6			
Ghezzi #37712	Gastric Ca. Metast. liver		5.2		5.3	5.4	5.4	5.6			

TABLE II.

		NORMAL GASTRIC SECRETION ALKALINE TIDE.									
NAME	DIAGNOSIS		GASTRIC ACIDITY			PH URINE					
			Free	Total		Fasting	1hr.	2hr.	3hr.	4hr.	
Johnson #37851	Atroph. arthritis	20	13		5.6	6.1	6.8	7.7	7.6	7.7	
Blancoavilla #35017	Anxiety neurosis	59	109		6.2	7.6	7.7	7.9	8.3	7.1	
Roach #37269	Neurocirc- ulatory asthenia	80	82		6.9	8.2	6.7	7.2	7.4		
Mayer #29150	Arterioscl. cardiac failure	100	150		6.6	7.0	7.0	7.8	7.5	8.0	
Ryan #38580	Du. ulcer	55	80		5.7	6.3	6.8	7.7	7.0		
Cornelius #35922	Arterio- sclerosis	16	42		6.0	6.4	6.7	6.5	8.2	7.8	
Pulver #43405	Op. of splenic flexure	26	61		6.1	6.6	7.2	7.2	7.3	8.1	
Gordis #40697	C.N.S. Lesion	30	60		5.8	6.6	7.1		7.2	7.3	
Bunter #41303	Chr. Pul. tuberculosis	46	75		5.5	5.5	6.8	7.2	7.4	6.8	
Pratt #27089	Du. ulcer	45	80		5.6	6.5	6.4	7.1	7.3	7.0	
Lilly #36665	Hodgkin's Broncho- pneumonia	20	45		6.5		6.8		7.7		
Hoffman #39332	Du. ulcer	53	88		6.0	7.3	7.7	5.2	7.0	7.7	
Grody #41744	Atroph. arth. Arterioscl. heart dis.	15	30		5.8	5.8	6.8	6.8	6.6	6.5	
Fischer #39208	Dermatitis venenata Auric. fistula	66	85		4.8	5.0	6.2	7.0	6.7	6.7	
Dainer #38853	Chr. chole- cystitis Chole- lithiasis	4	30		5.0	8.4	6.5	5.2	5.4	5.0	

passed into the stomach by the nasal route and left in place during the five hour period. The fasting contents were entirely removed prior to the subcutaneous injection of 0.3 mg. of Histamine Phosphate and the drinking of the 500 cc. of water. About 15 cc. of gastric contents were aspirated at hourly intervals for the five hour period of the test. For the most part, gastric analyses and urine studies after the injection of Histamine were made on separate days to eliminate the nervous factor, although a sufficient number of examinations were made simultaneously to convince

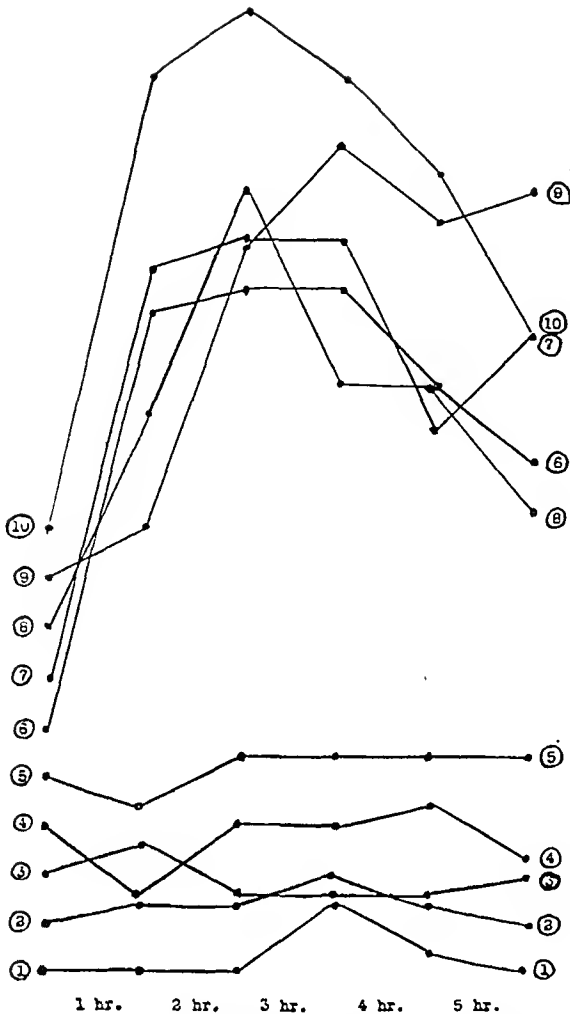


Chart 7. 10 curves—5 flat and 5 representing alkaline tides. The flat curves (1-5) no free acid.

us that the psychic factor does not demonstrably affect the results or their interpretations.

SUMMARY

In fifty patients presenting achlorhydria and the same number with relatively normal values for free HCl in the gastric contents, we found that with few exceptions, cases with achlorhydria showed no alkaline tide, whereas those with normal gastric secretion exhibited tides such as were observed in previous experiments with various test diets. (Charts 1, 4, 7, Tables I, II).

The few notable exceptions were as follows:

1. Cases with severe renal damage who failed to show the alkaline tide, even though free HCl in normal amounts was present in the stomach. Whether this procedure could be used as another test of renal function remains to be observed in our future studies. (Chart 2, Table III).

2. Cases with urinary infections were not suitable for the test because frequently a very alkaline urine persisted throughout the observations. (Table III).

3. An occasional patient had a distinctly alkaline urine very early in the morning, accompanied by a respectable level of gastric HCl, prior to the injection of Histamine. Although the value for free HCl might later increase considerably, there was not the degree of "alkaline tide" noted in most cases, and in fact, none might be noted. (Table IV). Very rarely an achlorhydric case presented a distinctly alkaline urine throughout the duration of the tests, the reason for which we had no explanation.

4. Patients who had inadvertently received medication before or during the test, might give results impossible of interpretation.

5. Cases with hypochlorhydria may fail to show the degree of alkaline tide found in patients with normal HCl secretion.

6. It is felt that extremely ill patients, particularly those with acute infections, cachexia, or very low blood pressure are not suitable subjects.

TABLE III.

RENAL INFECTION—RENAL DAMAGE NORMAL GASTRIC ACIDITY NO ALKALINE TIDE.

NAME	DIAGNOSIS	GASTRIC ACIDITY		Fasting	PH URINE				
		Free	Total		1hr.	2hr.	3hr.	4hr.	5hr.
Schubert #32930	Peripheral neuritis-pyuria-alk. urine	28-	35	5.9	5.8	6.0	6.0	6.0	6.0
Christ #63150	Chr. Nephritis Alb. R.B.C. Casts	36-	46	6.6	6.1	6.1	6.1	6.2	6.4
Brown #40665	Hepatic cirrhosis pus bact. fixed sp. gr.	36-	90	5.5	5.6	5.5	5.6	5.4	5.3
Lazarus #36847	Cholecystitis residual urine hypertr. prostate pus	65-	90	5.5	5.3	5.3	5.2	5.2	

TABLE IV.

ALKALINE URINES THRUOUT

FREE HCL FASTING

NAME	DIAGNOSIS	GASTRIC ACIDITY		PH URINE					
		Free	Total	Fasting	1hr.	2hr.	3hr.	4hr.	5hr.
Hubbards #40493	'Thyroid 'adenoma	10	75	7.1	7.6	8.4		7.1	5.3
Korthos #39228	'Du. ulcer	53	70	7.5	7.6	7.7	8.1	7.2	7.6
Durand #16594	'Peptic ulcer	15	55	7.5	7.9	7.8	7.6		7.8
Ford #35454	'Bronchial 'asthma	40	60	7.8	7.5	7.4	7.0	6.0	6.8
Parker #40748	'Urticaria 'Food allergy	32	90	8.5	8.5		7.0	6.6	
Mahar #40005	'Du. ulcer	22	42	7.2	7.6	7.7	7.8	7.2	7.5

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A Modification of the Hippuric Acid Liver Function Test

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IN the past fifteen years the subject of liver function engaged the attention of many clinicians, both here and abroad. Considerable literature has accumulated describing various liver function tests and the inherent advantages of each. It is not the purpose of this paper to enumerate the various tests nor to discuss their advantages or shortcomings, suffice it to say that to date no unanimity of opinion exists as to the most desirable method of testing liver function.

The importance of recognizing liver damage not only in diseases of the liver but also in diseases of other organs or in metabolic disorders, is a well established fact. Our attention has been called recently to the association of liver damage with toxic thyroid disease. The fact that postoperative thyroid crisis was due to hepatic failure, was amply emphasized, by various authors. In view of the above, the proper appraisal of the state of the liver as a guide to adequate therapy, is self-evident.

During the past year we have been employing on our gastro-intestinal service at the Beth El Hospital,

among other tests, the hippuric acid test described by Quick (1). The many favorable reports regarding this test have prompted us to adopt it and compare its value with the tests we have been using for the past number of years. The principle of the test depends upon the ability of the liver to synthesize hippuric acid, representing one of the several mechanisms by means of which the liver is capable of detoxifying substances brought to it from the intestine. The synthesis is accomplished by the conjugation of glycochol, which is elaborated by the liver, with benzoic acid absorbed from the intestine. In this test the patient ingests 5.9 grams of Sodium Benzoate dissolved in a half a glass of water, one hour after a breakfast consisting of coffee and toast. Immediately after taking the drug the patient urinates and thereafter separate hourly specimens of urine are collected for four hours. The specimens are then measured and acidified with concentrated hydrochloric acid, which precipitates the hippuric acid. After allowing the specimens to stand for one hour, the precipitate is filtered off, washed with a small quantity of cold water and allowed to air dry. After drying, the hippuric acid is either weighed or titrated with a 0.2 normal sodium

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TABLE I

Diagnosis and comparative figures given in twenty-five patients showing the results of the oral and intravenous methods

Patient	Diagnosis	Oral Method						Intravenous Method			
		Hourly Quantities Urine Voided in cc.				Total Benzoic Acid Excreted*	% Excreted	Hourly Quantities in cc.		Total Benzoic Acid Excreted	% Excreted
		1st Hour	2nd Hour	3rd Hour	4th Hour			1st Hour	2nd Hour		
1	Chronic cholecystitis. Hyperinsulinism	105	140	94	60	2.45 gms.	40%	45	55	0.95 gms.	48%
2	Toxic hepatitis	32	78	92	34	0.93 gms.	15%	42	48	0.33 gms.	15%
3	Chronic cholecystitis	155	120	81	28	2.85 gms.	47%	93	105	0.89 gms.	44%
4	Portal cirrhosis. Ascites	72	34	51	30	1.74 gms.	29%	49	28	0.51 gms.	25%
6	Ulcerative colitis	210	93	80	53	3.55 gms.	59%	98	104	1.22 gms.	60%
5	Chronic cholecystitis	84	155	115	42	2.62 gms.	42%	125	109	0.86 gms.	43%
7	Chronic gastritis	255	139	91	43	3.6 gms.	58%	75	35	1.29 gms.	64%
8	Diverticulitis of sigmoid	143	118	74	58	3.2 gms.	53%	74	29	1.31 gms.	55%
9	Menopausal syndrome	110	56	94	73	2.95 gms.	49%	55	36	1.25 gms.	52%
10	Hypothyroidism	125	144	108	50	3.8 gms.	53%	43	33	1.10 gms.	69%
11	Gastrectomy with probable hepatic metastasis	141	72	102	38	2.82 gms.	47%	98	104	0.99 gms.	49%
12	Duodenal ulcer	88	115	54	92	2.79 gms.	46%	86	72	1.3 gms.	66%
13	Chronic cholecystitis	132	141	100	61	3.55 gms.	60%	53	82	1.03 gms.	51%
14	Diabetic cirrhosis	63	101	143	69	3.4 gms.	56%	77	38	1.03 gms.	51%
16	Chronic cholecystitis	137	80	68	94	2.95 gms.	49%	91	53	1.11 gms.	55%
15	Chronic arthritis. Hepatomegaly	116	98	83	70	2.72 gms.	45%	59	54	1.16 gms.	58%
17	Toxic hepatitis	36	42	34	50	1.37 gms.	28%	43	41	0.51 gms.	30%
18	Menopausal syndrome	88	140	71	102	3.2 gms.	50%	51	34	1.27 gms.	53%
19	Typhus fever	72	148	68	84	3.08 gms.	50%	55	71	0.54 gms.	27%
20	Cardiospasm. Chronic cholecystitis	110	82	56	87	2.96 gms.	49%	60	30	1.25 gms.	52%
21	Myocardial failure	64	52	78	35	1.84 gms.	30%	53	53	0.52 gms.	31%
22	Toxic cirrhosis (apparently improved)	145	55	94	75	3.57 gms.	59%	72	65	1.15 gms.	57%
23	Chronic cholecystitis	74	112	58	118	3.05 gms.	51%	88	60	1.19 gms.	59%
24	Toxic hepatitis† (improved)	51	92	45	60	2.45 gms.	40%	38	33	0.87 gms.	43%
25	Common duct stone. Jaundice	182	25	75	35	3.52 gms.	55%	46	25	1.25 gms.	52%

*Original hippuric acid figures were converted and expressed in terms of benzoic acid.

†Results of a second test performed on patient No. 17, four weeks later.

hydroxide solution, using phenolphthalein as an indicator. To the amount of hippuric acid obtained one must add the amount of hippuric acid remaining in solution, which is 0.33 grams per 100 cc. of urine. The final figure is multiplied by 0.68 to convert the hippuric acid figure into benzoic acid, as it is generally reported. In case any specimen exceeds 125 cc. as quite frequently happens, it must be slightly acidified with acetic acid and boiled down on a water bath to about 50 cc. before precipitating the hippuric acid. The greater the volume of urine, the more dilute a solution does it become, and the less accurate is the precipitation of the hippuric acid in that given sample.

We have established to our satisfaction the fact that the test is very sensitive and of definite value in estimating the extent of liver damage in certain conditions. An appraisal of its value in the differential diagnosis of liver diseases, as compared with other liver function tests, will be reported in a future communication.

The procedure of the test as originally advocated, has certain disadvantages which may seem apparently trivial and yet they constitute definite drawbacks creating certain difficulties, which render the test less accurate in some patients. Lack of cooperation on part of the patient, willingly or otherwise, failure of the attendant to carry out instructions faithfully in administering the drug or collecting the specimens, increased quantities of urine in some specimens, making it necessary to concentrate the amount before proceeding with the precipitation, are some of the factors which complicate the procedure.

MODIFICATION OF THE TEST

It occurred to me that an intravenous method could be evolved whereby the test would be simplified and yet not detract from its accuracy. A modification of this sort in order to be ideal must fulfill certain criteria, namely:

1. A minimum amount of the drug to be used that would be compatible with accuracy.
2. Elimination of the "patient factor" as far as possible—administration of an accurate and full amount of the drug which cannot be lost by subsequent vomiting.
3. Ability to perform the test on a patient where vomiting is a presenting symptom.
4. Reducing the time required for collecting specimens.
5. Fewer and more concentrated amounts of urine to work with.
6. The test should be adaptable as a simple office procedure. The above criteria are fully met in the modification of the test which I am now to describe. The intravenous method was performed on twenty-five patients and in each instance a comparison was made with the oral method. The tests were done either one or two days apart.

PROCEDURE

In the morning, after withholding food and fluids for twelve to fourteen hours, the patient is made to empty the bladder, following which 20 cc. of a 10% solution (2 grams) of Sodium Benzoate* is slowly injected intravenously. Two, hourly specimens are then

collected and the hippuric acid determinations made in the same manner as in the original test. No untoward effects were encountered from the injection in any of the patients. It was found unnecessary to collect the urine beyond a two hour period, since, in the majority of the cases in this series with an unimpaired circulation, no hippuric acid was recovered after one and a half hours. Three of the patients displaying myocardial insufficiency manifesting right sided failure, showed a relative delay in hippuric acid excretion, but not beyond a two hour period.

COMMENT

A study of the accompanying table in which the oral and the intravenous methods are compared, reveals certain facts which indicate the advantage of the latter method and the parallelism in the final results between the two methods. This can be best appreciated by comparing the percentage figures of the respective methods. In the oral method a 40 to 60% excretion of hippuric acid (in terms of benzoic acid) is considered normal. Taking these figures as standards, we find that in the intravenous method, using two grams of sodium benzoate, the percentage excretion of hippuric acid with a normal liver function amounts to 40% to 65%. Expressing our results in grams it is apparent then that with the intravenous method an excretion of 0.8 grams to 1.3 grams would be considered normal. As may be seen from this table, the percentage excretion of hippuric acid with the intravenous method is generally higher, this is seen in 72% of the cases studied. This factor may depend upon the degree or state of intestinal absorption in individual cases. This discrepancy, however, is not significant if one method is used in following the progress of a given case. Case 19 a typhus fever patient was the only case in this series showing a marked variation with the two methods. The intravenous test done two days after the oral method, revealed definite liver damage. This may perhaps be explained on the basis of a marked toxemia.

SUMMARY AND CONCLUSIONS

A modification of the hippuric acid liver function test is herein described. The drug is administered intravenously instead of orally as in the original method. Certain advantages of this modification are pointed out, such as—smaller amounts of the drug used, better control of the amount of the drug given, no interference with the procedure in cases where vomiting is a factor, reducing the time necessary for collecting specimens as well as volume of individual specimens. The latter facilitates the laboratory procedure considerably. A comparative study of both methods was made on twenty-five patients, the close parallelism between the results obtained is indicated in the accompanying table. Using the new modification, a hippuric acid excretion (in terms of benzoic acid) of between 0.8 grams and 1.3 grams is found in patients with a normally functioning liver.

REFERENCE

1. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function. *Am. J. Med. Sc.*, 185:630-635, May, 1933.

*The solution in sterile ampules was generously furnished by the Loeser Laboratory, New York City, N. Y.

An Evaluation of Takata-Ara Reaction as a Liver Function Test

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CAREFUL scrutiny of the literature persuades us to realize that there is no single adequate test that would indicate efficiency of the hepatobiliary apparatus. The employment of a number of tests is therefore in concert with an organ which is endowed with many capabilities. In order to establish experimentally permanent liver pathology, recourse to a combination of methods becomes obvious. Thus, the Eck fistula for shunting the portal blood from the liver is conducive to liver atrophy, common bile duct obstruction impairs excretion of bile, and liver is made cirrhotic with carbon tetrachloride. It becomes apparent that each method impedes a particular function and depression of one function does not mean recession of another. The Takata-Ara reaction, regardless of its limitations, merits its inclusion among the many other liver function tests.

The enumeration of but a portion of the diversified functions of the organ serves to demonstrate their importance in the body physiology; glycogenesis, decomposition of amino-acids into urica, the maintenance of the colloidal composition of the blood serum, formation of bile, synthesis of hippuric acid, conjugation of phenol and indol into ethereal sulphates, thermo regulation, all of those and many other functions of the liver do not have the same clinical significance. This may be ascribable to one fundamental: the organ does not participate in all of them with the same specificity and intensity. A viscus wherein degenerative and reparative processes may go on simultaneously to a point of neutralization, and wherein a normal excretory activity is in keeping with a partially or even defunct detoxification mechanism, and thereby leading to an asymptomatic clinical picture, presents a situation replete with diagnostic confusions. The problem of distinguishing liver cirrhosis from neoplastic disease is often difficult to fathom. We are in agreement with Mann (1) who concluded: "While several of the tests may be of value clinically, it would seem that unless their use is combined with other methods of determining hepatic disease, they may cause serious errors." Any procedure added to other laboratory aids is worthy of close investigation. In comparison with the paucity of reports in American literature in respect to the Takata-Ara reaction, the European material is most impressive. Italy and Germany, in particular, furnish numerous investigations, mostly in connection with psychiatric clinics.

MECHANISM OF THE REACTION AND BRIEF HISTORY

This reaction was originally proposed by Takata and later by Takata and Ara in 1925, as a colloid reaction in chest fluid which would be useful in distinguishing typical pneumonic and tuberculous processes. They believed that it is the diminished stability of the serum proteins of the colloid system which makes precipitation possible with mercuric chloride-fuchsin solution. In aberration states the precipitation of the colloidal solution occurs. "It seems rational at this time," Wayburn and Cherry (2) write, "to be content with Staub and Jezler that the Takata reaction represents a dysfunction of the liver." Takata believed that the reversal of the albumin-globulin ratio by increase of the globulin fraction accounts for the reaction—a shift towards globulin in the serum. The lowering of the A/G ratio of the serum (if 2:1 ratio is taken as the normal) was believed to cause the reaction, according to Vigoda and Montanari (3) and Ragins (4). In agreement with Takata, Kirk (5) considered the rise in serum globulin as the essential factor in the reaction. A positive reaction was also ascribed to acidosis and dehydration in children by Recht (6) in agreement with the experimental work on rabbits by Allesandro (7) that a positive Takata-Ara correlated ketonuria. The mechanism of the reaction is still debatable by others. Schindel and Barth (8) found inconstancy between a positive Takata-Ara and either increase in the globulin factor or lowering of the A/G ratio. Schindel (9), in another publication, wrote that Jezler applied the reaction to the serum in patients with liver disease. The latter assumed that the mechanism of a positive reaction is caused by changes of the protein components and that an increase of the total proteins causes a change of color, while a disproportionate globulin increase produces flocculation. As the liver is chiefly responsible for protein metabolism, a shifting towards globulin would be indicative of hepatic disease. He found that cases with positive reactions had a marked diminution of the coefficient albumins: globulins. Schindel refers to Skouge's denial of the importance of such shifting of the protein coefficient. Schindel's observation is interesting, namely that no parallelism can be found between the reaction and the sedimentation rate in various diseases. Such findings are intriguing because rapid cell sinking is also attributed to an increase of globulin. Since the sedimentation rate is related to the A/G ratio, the displacement of which is a characteristic finding in cirrhosis of the liver, it is difficult for us to understand that in view of the well-known mathematical principle, things equal to the same thing are equal to each other, a sedimentation rate should coincide with a positive Takata-Ara

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reaction. Our series of cases, which will be discussed later, is too small for any conclusion to be drawn with regard to this particular point; yet, there seems to be a definite parallelism between a positive Takata and a rapid erythrocyte sinking. This opinion is in contrast to D'antono and Pollergini (10) who point to a lack of correlation between the results of the reaction and the sedimentation rate which parallels the A/G ratio. These authors showed that the positivity of the reaction does not correlate strictly with the displacement of the relations between the albumins and globulins in favor of the latter. Vigoda and Montanari (3) direct attention to Oliva and Pescasmona who obtained a positive reaction in a normal person after adding some globulin to the serum, and drew a negative result when they added albumin to the serum of an established cirrhotic. This experiment emphasizes the outcome of the test upon the protein proportions in the serum. Since the albumins are characterized by stability and the globulins by lability, it may be assumed that the former impede precipitation and the latter induce it. Wayburn and Cherry (2) write that "Medvei and Paschkis found that the addition of heparin had been shown by A. Fischer to convert serum albumin into serum globulin." Schindel (9) added lower fatty acids to a normal serum and produced a positive reaction and then by the addition of alkalis obtained a negative reaction in a serum previously proven positive. This experiment injects doubt in the globulin responsibility thesis. He reasons, however, that it is untenable that free acids could be present in the blood without shortly betraying their presence.

SURVEY OF THE LITERATURE

It has been assumed that the liver was the essential source of formation of the various fractions of the plasma, and that in cirrhosis, the globulin factors were on the ascent, the albumins on the descent. This judgment, according to Vigoda and Montanari (3), led to the belief that the study of these ratios might constitute an index of liver function. They refer to D'amato's statement that the inversion of the A/G ratio is contemporaneous with, and sometimes precedes other events concerning the function of the liver. Experiments have shown that the liver repairs losses of fibrinogen quite rapidly, while the losses in globulin, and especially of albumin are replenished only after delay. While during physiologic integrity the albumin quotient is almost double that of the globulin, decided reversal occurs during a phase of pathologic physiology. It must be held, therefore, that the clinical interest in these findings is confirmed by the use of the Takata-Ara reaction in the blood serum and in the ascitic fluid.

SPECIFICITY OF TAKATA-ARA REACTION

Cassiano (10) reviewed the results and the history of the reaction, its modification, application and interpretation by various authors and concluded that the reaction is by no means specific in respect to cirrhosis hepatica. In contrast, Magath (11) writes, "The impression is gained from the numerous papers published in Europe, and from the few now recorded in the American literature, that the test is thought to be fairly specific for cirrhosis, but that early in the disease the test is negative, and further, that the correlation between positive Takata-Ara tests and re-

versals of the A/G ratio is high." From his series of cases Magath maintains, it became clear that the reaction on serum is an empiric test, a colloidal phenomenon which has as yet not been explained. The test is not specific for either injury to the liver or cirrhosis, but in the presence of hepatic disease, a positive reaction is more likely to indicate cirrhosis than another disease. It becomes evident as one scans the literature, that the negative reactions were obtained in the earlier stages of hepatic cirrhosis, whereas in the advanced stages of cirrhosis, the tests were positive. Magath reasons, "That the test is not specific for cirrhosis is plainly evident, and if one can make use of the test at all in such diagnoses, it is just a matter of saying that, of the nonobstructive lesions of the liver, cirrhosis is the most common, and hence that there is more chance that the lesion under such condition is cirrhosis. Doubtless almost all advanced cases of cirrhosis will yield a positive Takata-Ara." Kirk (5) coincides with Magath that the reaction "was found to be positive in the serum and ascitic fluid in nearly all advanced cases of cirrhosis, and usually negative in all other diseases, including cholelithiasis and carcinoma of the liver." Ragins (4) in a study 276 patients, using the clinical picture as a basis for grouping diseases, substantiated whenever possible by post mortem findings and surgical biopsy, found that liver cirrhosis led the list. This author does not doubt the value of the test in hepatic cirrhosis, and reports it positive in 98% of the cases. Crane (12) pointedly draws attention to a group of 21 cases of advanced portal cirrhosis (Laenec), twenty of which yielded positive reactions in both serum and ascitic fluid. The one negative case was diagnosed as cirrhosis upon clinical grounds. In the follow-up of the positive cases to fatality, the reaction did not in any case tend to diminish in degree of intensity, but as the terminal stage of the disease appeared, the intensity of the reaction tended rather to augment, as judged by the amount of precipitation. As a corollary to the accuracy of a liver cirrhosis diagnosis, esophagoscopy disclosed esophageal varices in all but one. In all of the six cases of liver neoplasm, the reaction was negative. However, they were all cases of secondary hepatoma. According to this writer, the main objective of the reactions lies in its differential diagnostic value to distinguish between cirrhosis, liver neoplasms and other advanced hepatic disorders. Lazzaro (13) offers persuasive evidence that favors efficiency of the reaction: the reaction was negative in twenty normal persons (physicians and medical students). In sixty persons suffering from diverse diseases, the reaction was always negative. In 29 cases of Laenec's cirrhosis, in which the tests were repeated a number of times and the findings verified at operation or post mortem, the reaction was positive in 24 cases, slightly positive in three cases and negative in two, and in one of these (probably an early cirrhosis), the reaction, became positive in a later period. This one case of Lazzaro corroborates Jezler's contention that this reaction cannot be used for determining an early phase of hepatic cirrhosis. In agreement with these writers, Magath states, "Early cirrhosis quite evidently does not produce changes which result in a positive Takata-Ara test." Chasnoff and Solomon (14) performed the test on 48 patients with definite hepatic disease and on 27 in whom there was no clinical reason to suspect any

involvement of the liver. Their results are in accord with those of most investigators who maintain that the test is positive in advanced cirrhosis but may be negative in early cirrhosis. Heath (15) summarizes his results of the reaction in various hepatic disorders and numerous controls, and concludes that the reaction was positive in sixty per cent of seventy-seven cases of liver cirrhosis, and also in certain cases of marked liver damage. Perhaps a bit enthusiastically, the same writer also concludes that the test may be regarded at present as a specific liver function test, although it does not run parallel with other liver function tests. Likewise, Ragins (4) injects enthusiasm in the reaction by asserting that the test is positive in 98% of the cases of cirrhosis of the liver, and that the simplicity of the test warrants its use both as a diagnostic and prognostic aid in hepatic cirrhosis. Lazzaro pointedly notes that in two instances, the flocculation increased in keeping with accentuation of the condition, the converse held true during convalescence, the reaction became negative and also the A/G ratio changed to higher values. An inversion of the A/G ratio was found in all positive cases. Magath (11) found a correlation between the Takata-Ara and a reversal of the albumin globulin balance in 83% of the cases, and pointedly stated, "A reversed albumin-globulin ratio occurs about as frequently in cases of hepatic disease as does a positive Takata-Ara Test." Luchi and Manfredini (16) showed that the test had been positive in all cases of hepatic disorders. The ascitic fluid in these cases proved positive. In their cases of carcinoma of the liver, the reaction was negative, except for three, in which the symptomatology was dominated by neoplasia associated with icterus and cirrhosis, an element unsuspected previously, and which was verified at autopsy. Rappolt (17) described the results obtained with the reaction on 348 patients with suspected hepatic disorder. Of the patients in whom liver cirrhosis was certain, 85% had a positive Takata. She concludes in concert with others, that the reaction is a valuable diagnostic aid in differentiating hepatic cirrhosis from other liver disorders. Greene (18) avers that Takata is not specific in hepatic lesions, since a persistent reaction may also be obtained in the serum of patients with multiple myeloma. He points to the lack of correlation between the type of pathologic lesion and the function which is disturbed. The writers accede to this thesis which explains, to a degree, the non-specificity of a reaction, directed to an organ, that is both a manufacturing as well as an excretory unit; multiplicity of maladies accounts for non-uniformity of the reaction in known cases of parenchymatous liver damage. In the same vein, Biondo (19) reflects on specificity because of the test positivity in a diversity of maladies. In respect to prognosis, however, he refers to the belief of many authors that the reaction has an important prognostic value in affections of the liver, and that an increase in flocculation in the course of a cirrhosis indicates an aggravation of the condition.

Analysis of the literature surveyed showed the following to have been discussed:

1. Relative simplicity of the performance of the test.
2. Degree of specificity.
3. The decreased stability of the colloid system which makes precipitation with mercuric chlorid-fuchsin solution possible.

4. Increase of flocculation in relation to the gravity of the affection.

5. The significance of a disturbed A/G balance in relation to the reaction.

6. Protein concentration in relation to positive Takata-Ara reaction.

7. Prognostic value of the test.

It is evident that the research was directed principally toward determining the composition of the proteins of the blood serum, and that the liver is the main source of protein fraction genesis. The relation of its constituents might build up an index of liver function and Takata-Ara reaction in the blood serum and in the ascitic fluid confirms the clinical aspect in these findings. There seems to be a consensus of opinion as to the theory upon which the test was based. There is an agreement that the sedimentation rate parallels the A/G ratio, but a paucity is apparent in correlation between sedimentation rate and the reaction. Specificity of the test in respect to liver cirrhosis is refuted by some authors and pointed to positivity of the test in liver cirrhosis by others. It was brought out that a high percentage of positivity was obtained in those cases when hepatic disease was unassociated with other affections. Negativity of the test featured liver neoplasms. Crane and Lazzaro take a uniformed stand in favor of the reaction as an aid in the evaluation of such two divergent maladies as hepatoma and cirrhosis. It is generally agreed that the values of the test in the incipient phase of cirrhosis is frequently negative. Although there is a palpable flexibility between the various investigators as to the merits of the reaction, the impression gained by the writers is, that the subject matter radiates encouragement for its employment to assist us in the establishment or refutation of the diagnosis of liver cirrhosis, particularly when in association with other liver function tests. As regards prognosis of liver disease in relation to a positive reaction, it was argued that, since a positive test may indicate a more severe grade of liver damage, the test is of more value in prognosis than in diagnosis, as the reaction pointing to prognosis became less positive and even negative with clinical amelioration.

MATERIAL

Our material comprises a close study of ninety-four hospital records. The cases were labeled among other final diagnoses, as Atrophic Cirrhosis of the Liver. In some of the cases, the diagnosis was based on clinical criteria; on others on combined, clinical, laboratory aids, punch biopsy and autopsy findings. The data was analyzed and correlation sought between some of the liver function tests and Takata-Ara reactions. Seventy-two Takatas were done, fifty-three yielded positive reactions and nineteen were negative. Two cases diagnosed as hypertrophic cirrhosis of the liver yielded negative reactions. Four cases, in which punch biopsy was done, were labeled cirrhosis of the liver. In one, no Takata was done, and in the other three, the reactions were positive. Six cases, which were recorded "atrophic cirrhosis of the liver, died, no autopsy," yielded positive Takatas. In several cases, the Takatas were first negative and later became positive. In some of the cases, the reaction was repeatedly positive. Twenty-six cases with a final diagnosis of Alcoholic Cirrhosis of the Liver gave positive reactions, twelve

of these had a reversal of the A/G ratio, five had a 1-1 ratio and nine a normal A/G ratio.

It is interesting to note that in one of these cases, which yielded a positive reaction, and had a normal ratio, contrasted with a high blood sedimentation rate, punch biopsy revealed "fatty degeneration of the liver. Patient died." Another case in which there was a reversal of the A/G ratio, the punch biopsy disclosed "alcoholic and fatty cirrhosis." Eleven cases with a final diagnosis of alcoholic cirrhosis of the liver gave a negative reaction; five of these had a 1-1 ratio; five a normal ratio; one a reversed ratio. All three were discharged "improved." The role played by multiplicity of vices is interesting. Thus: where the history registers "moderate" to "heavy drinking" and in these cases a Wassermann was done, the impression one gets is, that, when Takata was positive, Wassermann was either doubtful or negative and the converse seems to force itself into notice; in four cases clinically diagnosed as atrophic cirrhosis of the liver, the Takata was negative, but their Wassermanns were four plus. It is regrettable that no routine serology was obtained in the material under discussion, for not all cases which were tested for Takata were routinely tested for Wassermann. We may point to symbiosis—a phenomenon which accounts for a divergent etiology and a convergent pathology. Thus: either syphilitic hepatitis and toxic hepatitis might eventuate into replacement fibrosis. The Takata-Ara under such circumstances, however, is apt to be negative rather than positive.

A few of these cases invite comment.

Case: Hepatoma with cirrhosis of the liver, with consecutive positive Takatas. Ascites in the presence of a normal serum proteinemia. The non-parallelism between ascites and serum protein may be ascribed to the other autopsy findings in the case: "Hemoperitoneum and Hemorrhagic Pancreatitis." Is it not conceivable that the total serum protein through absorption raised the total proteins in the blood plasma to normalcy? Significant, however, is the reversal of the A/G ratio; albumin 2.67; globulin 3.35; ratio .80; thus implying failure of the liver to furnish albumin and conducive to fall of colloid osmotic pressure of serum, a situation which favors transudation.

Case: Banti's Syndrome. Chronic Perihepatitis with Hyperplastic Hepatitis. Takata-Ara negative. The negative Takata would be in concert with hyperplastic hepatitis and in harmony with the cholesterol and cholesterol esters values (227-146). The cause of death in this case, "Internal hemorrhage from varicosity of esophagus." Esophageal varicosity implies a compensatory phenomenon and harmonizes with the abdominal fluid in this case, (many monocytes, many epithelial cells, lymphocytes, no evidence of malignant cells), designating a decompensating atrophic liver cirrhosis. With Banti's disease, the situation may be designated as hepatosplenomegalic cirrhosis. Where the dominating hypertrophy in "Intra-lobular form of cirrhosis" over atrophy in "Perilobular connective tissue proliferation," terms utilized by Klempner (20) in classifying cirrhosis is the situation, the expected reaction would seemingly be negative. The cause of death in this case grossly supports atrophic, final phase of hypertrophic cirrhosis. This case demonstrates a concomitant histopathology and accounts for a concomitant icterus and ascites. This patient was a male, age 56, heavy drinker, swelling of the abdomen of eight years' duration, icteric for two months. To reconstruct the clinical sequence of events from a study of the post-mortem findings, hepatosplenomegalic cirrhosis terminating in atrophic cirrhosis, makes, we believe, a compelling diagnosis.

BROMSULPHTHALEIN TEST WAS DONE IN THIRTEEN CASES

Eleven cases with quantitative values ranging between lowest, 25% to highest, 100% retention, yielded positive Takatas. One with 10% retention of the dye and one with practically no retention gave negative Takata reactions. The series is too small to draw a conclusion, but nevertheless, compliments the Takata-Ara reaction.

SERUM PROTEIN CONCENTRATION AND ITS INFLUENCE ON TAKATA-ARA REACTION

In twenty-seven cases with positive reactions, the highest concentration of serum protein was 8.41 mg. to 100 cc. of blood serum, and the lowest of total serum protein 4.58 mg. to 100 cc. In a group of thirteen negative reactions, highest concentration was 7.86 mg. to 100 cc. of blood serum; lowest, 4.27 mg. to 100 cc. of blood serum. These figures demonstrate, to a degree, that neither a hyperproteinemia, nor a hypoproteinemia has any influence on the positivity or negativity of the Takata-Ara reaction, and favors the independence of the test with respect to the protein values in the blood plasma. Butt (21) writes, "Hypoproteinemia in certain diseases of the liver is well known, and here again the low level of serum protein often is intimately related to the formation of edema and ascites." In a group of eight cases of ascites, in which protein values were obtained, the results are in contrast with Butt's statement. Thus, the highest concentration was 8.41 mg. to 100 cc. of blood serum, lowest 5.42 mg. to 100 cc. of blood serum—lowest accepted values which constitute hypoproteinemia are less than 5.5 mg. to 100 cc. of blood serum. Three of these showed a reversal of the A/G ratio. As alluded to, cases were encountered which showed a normal proteinemia (protein value) with a positive Takata; conversely, a normal total protein and a negative Takata with an unusual ascites. The following are two representative cases:

Case 1. A male, aged 65 years. The autopsy findings revealed a hepatoma with hepatic cirrhosis and hemoperitoneum. In this case, though speculative, it is highly suggestive that the hemoperitoneum has raised the serum protein through absorption of protein into the blood serum.

Case 2. A female, aged 39 years, multipara (seven children). Admitted excess alcohol intake. She entertained a very excellent appetite. Her protein intake was adequate. The non-parallelism between her ascites of a marked degree (size of the abdomen over-hanging sides of the bed), and a normal serum protein was noted. She had a three plus leg edema which disappeared with tapping of 26 quarts of ascitic fluid.

We believe, with regard to the above case, that the adequate protein ingestion, good appetite, normal absorption (from the gastro-intestinal canal clinically estimated) no loss of protein in the urine, and the raising of the osmotic pressure of the serum through acacia therapy which tended to retain some of the fluid within the capillaries, are the factors operating to account for this apparent paradox; namely, ascites in the presence of a normal protein with no reversal of the A/G ratio and a negative Takata-Ara. Another factor we must consider in our assessment of a negative Takata with other criteria of a clinical amelioration is the great capability of the organ toward

anatomical regeneration, by virtue of which degeneration is compensated and is clinically obscured through the establishing of a point of neutralization. From a general survey, however, it becomes apparent that it is the reversal of the A/G ratio more so than the hypoproteinemia that engenders to the positivity of the reaction. Our cases demonstrate as follows: fifteen cases, which yielded positive reactions and a normal proteinemia, showed a reversal of the A/G ratio; five cases gave a 1-1 ratio; and nine cases gave no inversion of the ratio.

The series is too small to warrant conclusions. The writers are, however, inclined to agree with the Japanese investigators who thought the reaction ascribable to changes in the relative amounts of albumin and globulin in the serum with the latter in excess, so that the colloid was no longer protected, a phenomenon dependent on a reversal or partial reversal of the ratio of A/G. To quote Butt (22), "In diseases of the liver, the colloid osmotic pressure and the concentration of proteins in the serum frequently are low. It is assumed that this is the result of the failure of the liver to manufacture the required amount and type of plasma proteins." In support of our contention that it is not the total serum protein that heralds liver pathology, Butt pointedly writes, "In eight out of twenty cases of diseases of the liver in which ascites and edema were present, the colloid osmotic pressure was low but the serum protein values were within normal limits." However, we also must note that a moderate reduction in the serum proteinemia occurs in the more advanced phases of chronic liver diseases. Hypoproteinemia must be ascribed to a deficient production of protein by the liver, particularly where nutritional disturbances and loss of protein in ascitic or edemic fluids in decompensated cases can be ruled out. Out of nine of our cases of ascites with positive reactions, five had a normal total serum protein and four had a hypoproteinemia of less than 5.5 mgs. per 100 cc. of blood plasma. Two cases of ascites with a negative reaction yielded a normal protein value.

TAKATA REACTION AND BLOOD SEDIMENTATION RATES

Strongly positive Takatas were shown associated with marked increase in rate of erythrocyte sinking. Seventeen cases yielded, simultaneously, acceleration in cell settling and positive reactions. Three cases yielded non-acceleration in erythrocyte sinking and no reversal of the A/G ratio. In sixteen, the sedimentation rate ranged between 21 mm. in one hour to 162 mm. in one hour. Four of these had a 1-1 A/G ratio, five had a reversal of the A/G ratio, one had a marked hypoproteinemia, and the remainder gave a normal serum proteinemia with a normal A/G ratio. A different genesis for the two tests becomes apparent: in the Takata-Ara, the positivity of the reaction is ascribable to a reversal of the A/G ratio, whereas the sedimentation rate is governed by the increase in fibrinogen. The discovery by Macfarlane of a case whose blood contained no fibrinogen offered Okley (23) the opportunity of studying the relationship between this substance and erythrocyte sedimentation rate. Thus, the addition of blood of varying fibrinogen content, to the fibrinogen minus blood, has raised the sedimentation values of the mixed blood, proving that fibrinogen plays a large and probably the largest part in influencing the sedimentation rate of human blood.

We may suggest that a dissociation of liver function with respect to a similar pathology is probable, and thus account for two tests based upon a divergent genesis but involved in directing attention to one disorder.

DISCUSSION

The essential factors which emerge from our study of the Takata-Ara reaction are, we believe, encouraging its inclusion into our diagnostic armamentarium. Our indulgence in its practice would obviate the uncertainty which tended to lessen its value in diagnosis. After all, the tree bears fruit only when permitted to develop. The conquest of any test is not by struggling against it, and surely not by running from it, but by diligent pursuant observations. Cirrhosis hepatica need not be the only culprit to give us a positive T.A.R. The same fate besets other adequate liver function tests. Specificity need not be a requisite of the test. Ottenberg (24) informs us that the impression at Mount Sinai Hospital is that the reaction is of some, but not very great, diagnostic use. Yet, he pointedly writes, "It is almost invariably positive in typical cases of cirrhosis of the liver and in the great majority of acute degenerative liver diseases." In the same vein Baehr (25) states, "On the whole, it has been a fairly reliable test for cirrhosis of the liver, although not infallible." We may point to circulatory bankruptcy with chronic passive congestive hepatitis, yielding a small percentage of positive reactions, and to Jezler's (26) eighteen cases of acute glomerular nephritis, fifteen of which yielded positive reactions. Wayburn and Cherry (2) draw attention to occasional positive reactions found in miscellaneous diseases, and cite subacute bacterial endocarditis and lung abscesses, one out of seven in the former, and one out of five in the latter. In agreement with Jezler, they mention three cases of acute glomerular nephritis and one acute flare-up of chronic glomerular nephritis, all of which gave positive reactions. On the other hand, all of their 24 other cases of chronic glomerular nephritis gave negative reactions. With respect to the degree of the reactions they obtained, they note, that the subacute cases gave reactions of a weak variety; the acute gave, presumably, conventional results, and all of the chronic cases gave negative reactions. This, we believe, points to acuity and severity of a pathologic process which embraces the factors concerned in yielding a positive reaction. An early or quiescent phase of hepatic cirrhosis also accounts for negativity of the reaction, and from this angle the test merits clinicolaboratory respect, since considerable liver damage must be present before the test becomes positive. Also, since the functions of the liver operate more or less independently of one another, no single test can be of much value, particularly when found to be negative. We must rationally conclude non-specificity of the test. If, however, we could describe the test as being relatively specific, we would then compare the test to the Wassermann in syphilis, which may also occur in non-luetic conditions, and its detection routinely searched for, would prove to be of vital importance to a proper evaluation of a condition. Cases are encountered where the addition of the Takata fortifies the diagnosis of cirrhosis largely based on other liver function tests, thus making the diagnosis of liver cirrhosis more definite. When retention or non-obstructive icterus is to be differentiated from regurgitation

or occlusive icterus, all other tests pointing to the former—a positive galactose, urobilinogen in the urine, a clinical picture depicting cirrhosis—a positive Takata differentiates surgical from medical jaundice, particularly when jaundice is painless.

In cases in which one function may be impaired and another intact, the positive reaction favors a diagnosis of liver cirrhosis. Two of our cases yielded a normal galactose test, but high retention of bromsulphthalein and a positive Takata. Twelve of our cases all yielded positive Takatas with normal values of cholesterol and esters in some, and high in others. It may be stated with some degree of certainty that extra hepatic obstructive processes without much liver damage do not result in a positive Takata-Ara and therefore aid us in differentiating an intra from extra hepatic disease, unless, a parenchymatous liver damage is concomitant with extra hepatic obstruction. It must be admitted that the correlation between positive reaction and a reversal of the A/G ratio is high, and since the positivity of the test depends upon the elevation of the globulin level, the reaction is likely to be positive in any disease in which a protein shift occurs. Non-specificity does not differ in respect to Takata from the non-specific character of the erythrocyte sedimentation test in various maladies, Wassermann in syphilis, and heightened blood urea in chronic glomerular nephritis.

Regretfully, our cases of liver carcinoma were not subject to the Takata-Ara test. Wayburn and Cherry (2) recorded 37 cases of primary and secondary carcinomatous invasion of the liver. All gave uniformly negative reactions with one exception; a clinically diagnosed breast carcinoma which showed on autopsy, a wide spread carcinoma with proliferation of dense fibrous tissue in the region of the portal spaces and yielded a Takata reaction of .02333000. We may argue that the course of carcinoma by comparison to that of atrophic cirrhosis hepatica is too short to allow for replacement fibrosis to occur, and Takata deductively would be negative, and would aid us in differential diagnosis between malignant hepatoma and cirrhosis. Adding to a negative Takata a rapidly accumulating ascites and a short clinical course, particularly appearing in early life, the diagnosis of primary liver carcinoma would stand substantiated. On the other hand, a primary carcinoma in advanced age may be regarded as having developed in an organ which harbored cirrhosis as an antecedent lesion. Since the presence of cirrhosis is requisite for a positive Takata, it would be interesting that an investigation should be directed to establish negativity or positivity of the test in primary liver carcinoma in aged individuals.

The writers feel that in preoperative cases, particularly in right upper abdominal quadrant pathology, we should utilize the evaluation of either a positive or negative result of a T.A.R. on a par with the hippuric acid test. Both of these tests are being sadly neglected. It seems reasonable to assume that a positive reaction

and a positive decrease in hippuric acid synthesis, would help to differentiate an obstructing painless jaundice from the painless icterus in portal cirrhosis, acceding, of course, to the rarity of jaundice in cirrhosis. A correlation of positivity between these two tests would offer evidence against surgical jaundice. Where surgery is imminent, the discernment of a latent chronic hepato-renal insufficiency—low in hippuric acid output, and a low urica clearance—would augur, preoperatively a post-operative upheaval, which, on clinical examination alone, does not reveal a latent hepato-renal lesion. We are not looking to the laboratory for mastering but serving our clinical sense.

We may emphatically stress that the development of the test to the stage in which it operates is intriguing, and points to the advisability of holding on to it, hoping it will serve us if not to the capacity of specificity, at least guide us in concert with other liver function tests, to enhance precision in clinical medicine.

CONCLUSIONS

1. The Takata-Ara test is of value in hepatic affections in general, and in cirrhotic forms in particular.
2. It has a practical value in cases in which the symptomatology is doubtful or incomplete.
3. The test is easy to perform and not difficult to interpret in the light of other liver function tests. It merits the same consideration as other tests.
4. Factors are encountered which limit its diagnostic value from the standpoint of specificity, but none to render it valueless.
5. The positivity of the test at a time when the pathologic alterations are considerable does not militate against its inclusion into our laboratory work-up of a case.
6. Since clinical signs often fail to indicate which function of the liver is first involved, we must recognize the lack of correlation between the type of pathologic lesion and the function which is disturbed.
7. Specificity cannot be attributed to the reaction, analogically, as none may be ascribed to the erythrocyte sedimentation and other tests.
8. Takata-Ara reaction is based on complex processes, and is under the influence of various factors which account for lack of uniformity of opinion. According to some workers, the A/G quotient is equal to 1.0 in a positive T.A.R., and according to others, it varies between 1 and 1.7.
9. Although the T.A.R. is positive in a fair percentage of cases of liver cirrhosis, its chief value is in differential diagnosis, and in its support of other liver function tests.
10. In early cirrhosis, the T.A.R. may be negative to become positive as the pathology advances, and regresses in concert with clinical amelioration.
11. Positivity of the T.A.R. turning to negativity implies favorable prognosis.

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The Proposed Phenolphthalein Test for Determining the Presence of Gastro-Intestinal Lesions. Results in Ninety-Four Cases.

By

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WOLDMAN'S (1) preliminary report of a proposed simple test for determining the presence of gastro-intestinal lesions was impressive, both because of its simplicity and its low percentage (3%) of error. The test was applied immediately as an accessory test in the study of gastro-intestinal cases. However, many results were in conflict with symptoms and signs and findings obtained by recognized

used instead of porcelain evaporating dishes. Two, four and six hour urine specimens were examined, the six hour examination being discontinued after it had

TABLE II

Results of the phenolphthalein test in patients with non-gastro-intestinal disease

TABLE I
Results of the phenolphthalein test in patients with gastro-intestinal disease

Diagnosis	Cases	Result	
		Positive	Negative
Functional Disorders			
Gastric Neurosis	2		2
Gastro-Intestinal Disease, type undetermined	1		1
Mucous Colitis	1		1
Total	4		4 (100%)
Organic Diseases			
Esophageal Varices, Bleeding	1		1
Duodenal Ulcer	6	1	6
Gastric Ulcer	1		1
Gastritis, Chronic	2	1	1
Carcinoma, Rectal	1		1
Colitis, Ulcerative	1		1
Total	12	2 (16.7%)	10 (83.3%)

procedures. Hence, the test was investigated more critically. It was ordered routinely on all admissions on the medical service of the Gallinger Municipal Hospital. The procedure for running the test was that recommended by Woldman. The urine was examined immediately after its collection, in order to eliminate the possibility of break-down of the conjugated phenolphthalein. The chemists' spot-plate was

Diagnosis	Cases	Result	
		Positive	Negative
Aortic Regurgitation	1		1
Abscess, Pericarditis	1	1	
Acholeluric Jaundice	1		1
Alcoholism, chronic	1		1
Anemia, Pernicious	1	1	
Aneurysm, Aortic	2	1	1
Arteriosclerosis, General	3	1	2
Arteriosclerotic Heart Disease	1	1	
Arthritis (various types)	7	1	6
Beriberi	1		1
Bronchiectasis, chronic	1		1
Bronchitis, acute	3	1	2
Carcinoma, Bronchogenic	1		1
Carcinoma of Prostate	1		1
Cholelithiasis	1		1
Cirrhosis, Portal	3	1	2
Cystocele-Rectocele	1		1
Dermatitis, Arsenical	1	1	
Food Poisoning	1		1
Glomerulonephritis, chronic	1		1
Hemorrhage, cerebral	2	2	
Hemorrhage, uterine	1	1	
Herpes Zoster	1		1
Hypertensive Heart Disease	8		8
LaCrippe	1		1
Lead Poisoning, chronic	1		1
Neurocirculatory Asthenia	1		1
Paralysis Agitans	1	1	
Pneumonia, lobar	4	1	3
Pleurisy	2		2
Pott's Disease	1		1
Psychosis	1		1
Singultus	1		1
Syphilis, Meningo-vase.	1	1	
Syphilis (Parasitis)	2		2
Thrombocytopenia, essent.	1		1
Tuberculosis, pulmonary, active	12	3	9
Pyelitis, acute	2		2
Pharyngitis, acute	1		1
Calculus, renal	1		1
Total	78	18 (23.3%)	60 (76.7%)

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been consistently negative in the first fifty cases. Any color from a pale pink to a dull brick-red was considered positive. See Tables I and II for results obtained.

It should be emphasized that, almost without exception, the tests were made before the investigator knew, or even suspected, the tentative diagnosis of each case. Further, the diagnoses given in Tables I and II are the final diagnoses recorded on the charts, after the patients had been through a thorough diagnostic study.

Only a few remarks are necessary in discussing the results. First, all cases studied presented symptoms

TABLE III

	Cases	Result	
		Positive	Negative
Tables 1 and 2 Combined	94	21.1%	78.9%
Fantus and Dyniewicz (2) Series	150	21.5%	78.5%

N.B. Fantus and Dyniewicz varied their doses (1.5-3 grains). The dose used in this report was 1.5 grains.

and signs sufficiently severe to warrant hospitalization. Second, in the case of bleeding esophageal varices and in three of the cases of duodenal ulcer, gross blood was present in the vomitus or in the stool, or both, as determined by the guaiac test; but in only one of these cases was there a positive phenolphthalein test. Third, the case of ulcerative colitis was obvious by sigmoidoscopic examination, but the phenolphthalein test was negative three times by mouth and twice by giving the drug as a retention enema; the guaiac test was positive, and the patient experienced exacerbations of symptoms each time the drug was adminis-

tered—pretty good proof that the drug reached the lesions. Fourth, the test was negative when the drug was administered in the barium meal and barium enema in a case of pellagra that gave a 4-plus guaiac test on four different days. (This case is not included in the statistics of this study, however, because of the modification in administering the drug).

SUMMARY

1. The proposed phenolphthalein test for determining the presence of a break in the continuity of the gastro-intestinal mucous membrane was studied in ninety-four patients hospitalized for diagnostic study and treatment.

2. In the series reported, the test was repeated in several cases making the total number of tests over one hundred and twenty, and the total number of examinations over two hundred.

3. The high accuracy of the test could not be verified.

4. The percentage of positives (21.1) in the entire series of cases corresponds very closely to that (21.5) reported by Fantus and Dyniewicz (2) in their series of 150 hospital cases at the Cook County Hospital, in which phenolphthalein was used for another purpose.

CONCLUSION

This investigation shows that the proposed phenolphthalein test is of no value in differentiating gastro-intestinal from non-gastro-intestinal disease, nor organic from functional gastro-intestinal disease.

I wish to acknowledge my thanks to Doctors Wallace M. Yater and Albert J. Sullivan for their valuable criticisms while this work was in progress.

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Treatment

INTRODUCTION TO THE SECTION ON TREATMENT

OFTEN the editor of a medical journal must wonder how much space he should give to clinical articles and how much to articles reporting the results of research. Among the readers there are two main groups, one of clinicians and the other of research workers, and when the men in one group are pleased, the men in the other group are likely to be dissatisfied. Some readers of this journal have expressed a desire for more articles that will help them in solving daily problems in practice, and particularly problems of treatment. In order to help such men it is proposed to run a column containing therapeutic suggestions which have recently appeared in the literature. Obviously the editors cannot vouch for the usefulness or sanity of all these suggestions: they can only pass on those bits of advice which sound interesting or promising or fairly reasonable. When warnings appear against dangers met with in the use of certain treatments these also will be noted.

Those readers who try out some of these suggestions and find them good or bad can help by briefly reporting their experience. Such reports will be welcomed and will be noted in this column. Brief reports of therapeutic discoveries will also be welcomed. They should be sent to Dr. Walter C. Alvarez, Rochester, Minnesota.

CHRONIC ULCERATIVE COLITIS

In the *Annals of Internal Medicine* for September, 1938, Bagen, Jackman and Kerr describe their treatment for chronic ulcerative colitis. They use serums and vaccines directed against the offending streptococci, and a high calorie diet rich in protein and low in residue. Sometimes they use repeated small transfusions of blood. They remove foci of infection. The

patient is kept in bed for a while and is given good nursing care.

They doubt if chemotherapy has much of a place as yet in the management of the disease. Calcium and parathyroid extract seem to be useless. Arsenic often does harm. Enemas containing azochloramid often irritate the bowel. Kaolin and aluminum hydroxide given per rectum may soothe the mucosa in the lower

end of the bowel in some of the milder cases. Histidine may help in a few cases.

In some of the milder cases sulfanilamide produced striking improvement, but in other cases no effect could be seen. The drug seemed to be of no use in the fulminating type of case in which therapeutic help was most needed. In four cases in which the drug had been used by others before the patient came to The Mayo Clinic, hepatitis with jaundice had appeared, and in three of these cases the patient went on and died. In another case, peripheral neuritis developed.

In some of the cases of unknown etiology vitamin concentrates and vitamin therapy in general have afforded striking relief.

A TREATMENT FOR ATTACKS OF ANGINA PECTORIS

Trichloroethylene which has for some time been used to relieve the pain of tic douloureux, has recently been recommended as a treatment for angina pectoris. It is being dispensed in little perles, to be broken so that the drug can be inhaled. The patient should be lying down.

THE EFFECT OF SOME DRUGS ON THE GALL BLADDER

In the January, 1939, number of the American Journal of the Medical Sciences, Schube, Myerson and Lambert report studies of the emptying of the gall bladder in man after the giving of benzedrine, atropine, and a combination of benzedrine and atropine. Benzedrine had no immediate effect on the viscus. Benzedrine and atropine together delayed the emptying of the gall bladder, but not so much as atropine alone did.

In a reprint received from Dr. L. Falla Alvarez, published in Vida Nueva, pages 320 to 330, 1938, the author notes that accidentally, while treating with Atabrine a patient with both malaria and lamblasis he discovered that the drug killed off the flagellates. He then found that P. Martin had reported a similar observation in Marseille Medical, volume 74, 1937.

A TREATMENT FOR HERPES

In the Archives of Dermatology and Syphilology for October, 1938, Kelly reported the treatment of herpes simplex and zoster with a 1:3000 dilution of moccasin venom given intradermally in doses of 0.2 cc. The results in herpes simplex were good, but those in herpes zoster were not so striking.

THE FOODS THAT COMMONLY BOTHER ALLERGIC CHILDREN

During the discussion of papers on allergy given at the meeting of the American Medical Association in 1938 and written up in the October 22, 1938, number of the Journal, page 1553, George Piness of Los Angeles, stated that among most pediatricians and allergists there is an idea that wheat is the commonest offender. On making a survey, however, of 1,000 histories at the Children's Hospital in Los Angeles, Piness found that wheat appeared to be fifty-fifth on

the list of offenders. In these children the commonest food to give both clinical and cutaneous reactions was tomato. Curiously, the most common cereal to give trouble was barley.

A number of those who joined in the symposium felt that the leukopenic index has little value in the identification of the foods giving trouble.

THE USE OF BILE TO IMPROVE APPETITE

Winfield reported in the September, 1938, number of the Journal of the Michigan State Medical Society that the giving of dried bile will sometimes bring back appetite. Also the giving of bile sometimes relieved the symptoms of belching, distention and constipation.

A DRUG WHICH MAY BE USEFUL IN CASES OF POSTOPERATIVE ABDOMINAL DISTENTION

In an article in the October number of the Proceedings of the Society for Experimental Biology and Medicine, page 135, Youmans and Waisman reported experiments on dogs with a Thiry fistula which indicated that beta-methylcholine-urethane, a drug which has been reported to have beneficial effects in cases of postoperative abdominal distention, caused a marked increase in the tonus and amplitude of rhythmic contractions in both the innervated and denervated jejunal segments of unanesthetized dogs. The drug tends to block inhibition of the intestine by sympathetic nerve stimulation. The effects of the drug were blocked by atropine.

LEAD POISONING

Gray and Greenfield in the New York State Journal of Medicine for October 15, 1938, advised against the use of large doses of calcium to "delead" patients with lead poisoning. It is likely to remove the lead too rapidly from the bones, and this may give rise to more damage of the nervous system. The authors advised the use of large quantities of phosphates which will help to produce an insoluble lead phosphate.

THE ACTION OF MORPHINE ON THE DIGESTIVE TRACT

In the American Journal of The Medical Sciences for November, 1938, there is an excellent review by Soma Weiss and Eggleston on the action of morphine on the body. Curiously, most observers now agree that morphine tends to increase the tonus and activity of the small bowel. The constipating effect seems to be largely an inhibition of defecation due perhaps to a loss of sensation in the rectum. The duration of the effect of an average dose of morphine on the intestine was about six hours both in animals and in man.

Those physicians who would like to avoid the undesired effects of morphine on the colon might well try Dilaudid, which often has no demonstrable effect on the digestive tract.

A NEW TREATMENT FOR HICCUPS

Shaine in the American Journal of The Medical Sciences, November, 1938, page 715, reported two cases of persistent hiccup in which benzedrine sulphate worked well.

A NEW TREATMENT FOR PRURITUS ANI

There have been several articles published recently, one by Hollander in the Archives of Dermatology and Syphilology for September, 1938, in which it is stated that pruritus ani can be treated satisfactorily by tattooing mercuric sulfide into the perianal skin. The

statement is made that this procedure brings a return of normal texture to the skin. We sincerely hope that others will find this treatment effective. It is always well in cases of pruritus ani or vulvae to inquire for causes of psychic strain because often the psychic causes seem to be highly important etiologically.

Editorials

GASTRITIS

IN view of the now widespread interest in gastritis, it may be worth while to call attention to the report of a little symposium on the subject held recently at The Mayo Clinic.

Dr. Robertson, the pathologist, commented on the fact that in this field the clinician and the pathologist have found it hard to meet on some common ground of understanding and nomenclature. He felt that both groups of men had doubtless been failing to pay sufficient attention to a number of important changes to be observed in the gastric mucosa. To him the outstanding anatomic peculiarity of the gastric mucosa is its rich capillary network with the marked changes which can from time to time take place in the size and fullness of these capillaries. As several observers have noted, the mucosa will be at one time pale and almost bloodless and at another time swollen and a deep red in color. Dr. Robertson quoted from the writings of Beaumont, who noticed frequent changes in the color, moisture, and general appearance of the gastric mucosa of Alexis St. Martin.

"In . . . undue excitement, by stimulating liquors, overloading the stomach with food—fear, anger, or whatever depresses or disturbs the nervous system—the villous coat becomes somewhat red and dry. . . There are sometimes found, on the internal coat of the stomach eruptions or deep red pimples . . . at first sharp pointed and red, but frequently becoming filled with white purulent matter.

"Diseased appearances, similar to those mentioned above, have frequently presented themselves, in the course of my experiments and examinations. . . They have generally, but not always, succeeded to some appreciable cause. Improper indulgence in eating and drinking . . . eating voraciously or to excess, swallowing food coarsely masticated . . . invariably produce similar effects. . . These morbid conditions are however seldom indicated by any ordinary symptoms, or particular sensations described or complained of. . . They could not, in fact, in most cases have been anticipated from any external symptoms; and their existence was only ascertained by actual, ocular demonstration. . .

"It is interesting to observe to what extent the stomach . . . may become diseased, without manifesting any external symptoms of such disease, or any evident signs of functional aberration. . . Extensive active or chronic disease may exist in the membranous tissues of the stomach . . . more frequently than has been generally believed."

To all of us physicians today the most significant and most to be remembered of the statements just quoted are those to the effect that often the morbid appearance of the mucosa *was not associated with any symptoms*.

Dr. Robertson spoke of the frequency of small hemorrhages in the gastric mucosa, and the fact that not infrequently these small hemorrhages, which are probably constantly occurring, give rise to ulcers. The repetition of such small injuries over the course of years probably serves eventually to leave a scarred or an atrophic mucosa.

The next speaker in the symposium, Dr. E. S. Judd, Jr., reported a histologic study of the mucosa from 278 stomachs removed at necropsy. With Dr. Robertson, in whose laboratory he worked, he recognized seven lesions of the mucosa: (1) accumulation of lymphocytes; (2) irregularity of the muscularis mucosae; (3) thickening of the muscularis mucosae; (4) fibrosis of the muscularis mucosae; (5) atrophy of the chief and parietal cells; (6) hyperplasia of the mucous cells, and (7) disorganization of the elements of the mucous glands.

Dr. Judd found that in all stomachs studied (200 with carcinoma and seventy-eight without) the commonest change in the mucosa was an accumulation of lymphocytes. The next commonest was an atrophy of the chief and parietal cells, and the next was hyperplasia within the mucous glands. In the control series of stomachs without carcinoma the next most common lesions, in order of frequency, were (1) thickening, (2) irregularity in, and (3) fibrosis of the muscularis mucosae. In stomachs from the younger persons there was mainly a thickening and irregularity of the muscularis mucosae with atrophy of the special cells of the mucosa. Hyperplasia of the mucous cells was seldom seen. The most nearly normal stomachs were found, as one would expect, in infants and children. Abnormalities in the mucosa were apparent already in stomachs from youths and young adults. Usually there was an accumulation of lymphocytes, probably of no great importance to health.

The important peculiarity of most carcinoma-containing stomachs was the presence, even in the mucosa far away from the cancer, of hyperplasia of the mucous cells. Judd's work confirms then the suspicions of others who have felt that the development of carcinoma in the stomach is commonly preceded by an old chronic gastritis due perhaps to many years of repeated insult by abnormal congestions and hemorrhages.

Dr. H. J. Moersch discussed the problem from the point of view of the gastroscopist. To him, one of the most difficult problems is to decide where to place the borderline between normal physiologic changes and those indicating chronic and permanent change. He felt that from the gastroscopic point of view gastritis may be divided into three types: first, the superficial or catarrhal type, due perhaps to acute infection or overeating or to the drinking of much alcohol. In these cases there is some edema and swelling of the

mucosa with increased secretion and perhaps small regions of superficial ulceration. Second is the so-called hypertrophic gastritis, characterized by infiltration of the mucosa, with stiffening in the rugae and a change in their pattern. There may be hemorrhages as well as superficial ulcerations. It is hard to know yet what relation these hemorrhages have to later ulceration. The third type of gastritis is the atrophic form with thinning of the mucosa. Interesting is the fact that one can encounter all types of gastritis in one and the same stomach, and it is not always easy to distinguish borderline types. Dr. Moersch was impressed by the frequent association of gastritis with organic gastric lesions.

Dr. Kirklin discussed the subject from the point of view of the roentgenologist. He felt that the inability of the roentgenologist to see signs of gastritis does not rule out its presence; the characteristic changes can be recognized in only a small percentage of cases. Obviously small mucosal changes cannot be seen, and mucosal atrophy can hardly be demonstrated. The most important and most frequent roentgenologic sign of gastritis is the presence of localized, ragged, irregular, hypertrophic mucosal folds. Wart-like granulations, mucosal erosions that can be demonstrated "en face," and pseudopolypous formations are so infrequently demonstrable that they have relatively little practical importance in the diagnosis of gastritis. Tangential projections on or near the lesser curvature, such as have been described, can be observed more frequently. When found, they constitute absolute proof of the presence of ulcerous gastritis. Indirect signs have to be interpreted with great caution and are significant only when associated with more definite findings.

Dr. Eusterman mentioned a type of gastritis often associated with achlorhydria in which the symptoms resemble those of ulcer. He felt that in most cases chronic gastritis is refractory to treatment, but gratifying cures have been obtained in cases of chronic hypertrophic, erosive or ulcerative forms and in some of the postoperative forms.

W. C. Alvarez, Rochester, Minn.

PERISTALSIS IS A CARELESSLY USED TERM

IF confusion is to be avoided it is essential that everyone who writes about the movements of the bowel use certain terms carefully and exactly. At present the term "peristalsis" is being used carelessly to mean any or all forms of motor activity in a segment of bowel. To begin with, this is flouting the dictionary. The American Medical Dictionary defines peristalsis, I believe correctly, as "a wave of contraction passing along the tube." The Oxford dictionary also speaks of "rhythmic wave-like contractions." The original Greek words *peri* and *stallein*, interpreted somewhat differently by different lexicographers, are stated by the Oxford authorities to mean "to send around."

Even those who are not interested in upholding the authority of the dictionary must be interested in seeing to it that every time a scientific term is used it means one definite thing. If peristalsis is to mean at times all forms of intestinal activity and at other times a traveling wave, confusion is bound to result. It would not be so bad if everyone agreed to use the term in its present-day omnibus sense because

then, when a man meant something definite, he would take care to use a specific term, such as "rhythmic segmentation," "swaying movement," "slowly-moving contraction," "systole," "wave," "tonus contraction," "reverse wave," or "slow transport of a bolus by shallow ripples." That much care is needed in this regard is shown me by the fact that as I write, I find myself committing again and again the very sin that I here decry.

A writer will sometimes use the terms *peristalsis* or *traveling wave* to indicate that the disturbance was traveling along the bowel, but it seems to me that the word traveling is tautologic because a wave must always travel. Perhaps it would be better to speak of the *normal waves* of the distal half of the digesting stomach instead of *gastric peristalsis*, which today may mean anything. Perhaps, also, physiologists could use with advantage the terms suggested by Cannon and others; namely, "diastalsis," meaning waves, or "katastalsis," meaning waves traveling caudad, and "anastalsis," meaning reverse waves traveling orad. I fear that it would be hard to introduce such new words into the language because unless the need is great or the words happen to strike popular fancy, they don't get taken up.

Walter C. Alvarez, Rochester, Minn.

A PROBABLE CAUSE OF MANY ABDOMINAL PAINS

UNFORTUNATELY, because of his early training, the average physician, when faced by the story of abdominal pain, rarely seems to think of an origin outside of the digestive tube. Anyone who sees many letters of findings and opinion sent with patients by family physicians and even consultants must be impressed with this fact. Actually, a large percentage of abdominal pains do not appear to arise in the digestive tract; they are not coupled with any phase of the digestive process, and it would seem that some of them must arise somewhere in the tissues surrounding the abdominal cavity: in the spine and in the muscles of both the anterior and posterior abdominal wall. It is probable also that some of the severe crisis-like pains arise in arteries and veins. There is no reason to believe that blood vessel pain is to be found only in the heart, legs and meninges (as in migraine).

Because of thoughts along this line we were delighted with a recent paper of Kellgren describing experiments on the production of pain in muscles, tendons and periosteum (Clinical Science, 3:175, 1938). To produce this pain Kellgren injected a few drops of a 6 per cent solution of sodium chloride into the muscle or onto its fascias. This solution produced a severe but transitory pain. As an experimental subject Kellgren used himself or occasionally a fellow student who was trained in the location and description of pains of various types. The work was done under the stimulating influence of Sir Thomas Lewis.

The first thing that was found was that 0.1 cc. of the solution injected into certain muscles such as the rectus abdominis or the small muscles of the hand caused severe pain, while the same quantity injected into the biceps or the glutei caused only slight pain. Occasionally when the solution came in contact with nerves another type of pain was felt. It was a feeling of burning and of pins and needles in the cutaneous distribution of the affected nerve. It was easy to distinguish this pain from that of muscular origin.

Fascial pains were also easily distinguished from pains originating in the skin.

Kellgren described in his article the ways in which the muscle pains radiated into certain regions where they were felt. In the case of certain muscles the injection produced a sharply localized pain, and in addition, a more diffuse pain. An injection into the muscle of the infraspinous fossa produced pain at the shoulder tip. Injection into the muscles often produced pain which was felt in a near-by joint. Irritation of the muscles of the sub-occipital triangle produced headache, while irritation of the occipitalis or the facial muscles in the region of the canine fossa gave rise to earache.

There were curious references of pain up and down the spine from irritation of some of the back muscles. In some cases pain produced in the oblique muscles of the abdomen was referred into the testes. The conclusion was that when saline solution is injected into a muscle, pain is referred to regions corresponding to the spinal segments from which its motor innervation is derived.

Each segmental region appears to consist of two parts: one in the back and the other in the front of the trunk. In the limbs these two parts seem to correspond with the anterior and posterior primary divisions of the spinal nerves. The pattern does not correspond with the sensory segmental skin patterns of Head or Foerster.

Pain arising at a point in the rectus abdominis was felt usually over several segments in front, while a

slight pain was felt in the back in a single segmental zone. It would be interesting to see how pain produced in the iliopsoas muscles is felt and distributed. Sometimes when a muscle was irritated, the region in which the pain was felt was tender to pressure, and this tenderness appeared to lie below the skin. Curiously, the referred pain felt after irritation of a muscle persisted in spite of anesthetization of the region with procaine. For instance, on injecting salt solution into the flexor digitorum, pain was felt in the hypothenar eminence and fifth knuckle, even after the ulnar nerve had been blocked at the wrist. Tenderness could be abolished by procaine block, but the pain remained unchanged.

The pain arising in muscle did not appear to be referred to areas of skin, but rather to deep structures such as joints or the testicle. Furthermore, the muscle pains appeared to be confused by the subject with pain arising directly from these deep structures. This suggested to Kellgren that the impulses responsible for the pain from muscle and from other deep structures follow a final common path in the central nervous system.

These studies show that a patch of myositis or perhaps a little hemorrhage into one of the muscles of the abdominal wall might easily produce a pain which would be referred by the patient, either deep into the abdomen, or else along aponeurotic attachments in groin or back.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

Les maladies de l'oesophage. By J. Terracol. Paris, Masson et Cie, 1938, 664 pages.

AT first glance, it would seem unlikely that anyone could write a book of 664 pages on the esophagus, but actually, Terracol and a group of seventeen collaborators have done it. What is more, examination of certain chapters like that on cardiospasm, shows that even more might well have been written. It gives one an idea of how enormous the field of medicine has become. The book is interestingly written and well illustrated. There are some colored plates showing the appearance of the diseased esophagus as seen through the electrically-lighted tube. There are bibliographies attached to the chapters, but unfortunately, there is no index.

The reviewer was disappointed to find so little on the treatment of cardiospasm. Actually, this should be the most complete and satisfactory section of the book because cardiospasm is perhaps the commonest trouble that the expert in this field is called upon to treat. The authors seem never to have heard of the Plummer dilator, which works so beautifully in these cases, and they give space to the old trans-abdominal operation, which should probably never be used any more. Certainly, if the book should go into a second edition, the authors should greatly strengthen the section on the treatment of cardiospasm. They should describe the Plummer technic and should show the tremendous advantage of passing the dilating instrument over a thread which has previously been swallowed and allowed to pass through the digestive tract.

Furthermore, instead of giving a number of possible modes of treatment, the authors should describe those that they have found useful and mention those which they feel should be placed in the discard.

But these criticisms should not obscure the fact that the book contains a tremendous amount of information and that it presents this information in an attractive way. Every medical library of any size should have a copy.

Spinal Anesthesia. By Louis H. Maxson, A.B., M.D., Seattle, Washington. Illustrated by J. B. Lippincott Company, 1938, Philadelphia. Price \$8.00.

THIS volume covers spinal anesthesia in a most thorough and painstaking manner.

Commencing with the history of spinal anesthesia the author takes one through an atomic consideration, the physics of this type of anesthesia, various drugs, contra indications and complications. The advantages and disadvantages of this kind of anesthetic are very carefully discussed and tabulated.

There is a very complete bibliography and index. The book is splendidly turned out, and should be read by both the anesthetists and the surgeons. One is amazed at the volume of detail found in the work and the reviewer feels that any surgeon who employs spinal anesthesia and the anesthetist who administers this type of anesthetic ought not to be without this volume in his library. This study by Dr. Maxson is a definite and helpful contribution to the art of anesthesia.

Anus-Rectum-Sigmoid Colon; Diagnosis and Treatment. By Dr. Harry Ellicott Bacon, B.S., M.D., F.A.C.S., F.A.P.S. J. P. Lippincott Company, Philadelphia, Pa.

Dr. Bacon has written an 800 page encyclopedic compend of present-day opinions and procedures in connection with diseases of the terminal portion of the colon and rectum.

The chief virtue of his book lies in the fact that apparently it reflects, graphically and in detail, not only his own opinions but the combined viewpoints of those who are known among American proctologists as the "Philadelphia Group." In Philadelphia and its environs, under the leadership of Dr. Collier F. Martin, a large number

of efficient men have limited their work to this specialty; practically all of them engaged in teaching and continuing throughout the years a close professional relationship with constant interchange of opinions.

The author has been able to express many of the sound and progressive results of this local situation in his book. In addition, the literature of the world has apparently been exhaustively studied and abstracted. The author has, however, made this abstract of value by personal comment and interpretation.

The book is written in sufficiently simple language to be of value to the medical student as well as the practitioner and the procedures described

are amply depicted by nearly 500 clear illustrations on suitable paper.

It is gratifying to know that completely anachronistic techniques and opinions are omitted from the volume, which is not a usual circumstance in text books of this size.

Curtice Rosser.

Abstracts

STURGIS, CYRUS C. AND GOLDHAMER, S. MILTON.

Macrocytic Anemia, Other Than Pernicious Anemia, Associated with Lesions of the Gastro-Intestinal Tract. *Ann. Int. Med.*, Vol. 12, No. 8, p. 1245-62.

Doctors Sturgis and Goldhamer have succeeded in clarifying the behavior of macrocytic anemia associated with dietary deficiency and gastro-intestinal disturbances and its response to anti-pernicious anemia treatment.

It is claimed by Castle that some unidentified "extrinsic factor" is ingested in the diet and this reacts with an "extrinsic factor" which is contained in the gastric secretions. As a result of this reaction a substance is formed which controls the rate of formation of red blood cells in the bone marrow. Since the red blood cells are not normally released until they are mature, any disturbance in the formation of the substance controlling the maturation of the erythrocytes will diminish the number which are released to the peripheral blood, and an anemia will develop.

The gastro-intestinal lesions which may be associated with a macrocytic anemia are total gastrectomy, extensive infiltrative carcinoma of the stomach, various lesions of the intestines such as stricture and anastomoses, and extensive liver disease which may be the result of widespread cirrhosis or some other process such as an acute hepatitis.

In many instances these cases yield to an anti-pernicious anemia medication—especially to the parenteral administration of liver extract. Iron usually is of no benefit.

The authors have reviewed a large group of pernicious anemia patients over a period of eleven years. A number of patients among those presenting themselves for diagnoses have illustrated the type of anemia which is under discussion here.

Ten case histories are presented with eight different conditions. All cases described are accompanied by a graphic chart of the hematologic response to anti-pernicious anemia treatment. A comprehensive table depicting the total data involved in the study is also presented. The radial drop in hemoglobin and erythrocytes following resection of the stomach

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and the subsequent rise with this treatment is striking.

In an interesting discussion the authors state that one reason which would indicate that intestinal lesions are responsible for this type of anemia is the disappearance of the anemia when the intestinal lesion is repaired. This series of patients also have very few of the symptoms accompanying Addisonian pernicious anemia.

The relation of liver disease to this type of anemia is thought to be a failure of the liver to function as a storage depot for the active principle which, as a result, cannot be released and therefore does not control the maturation of the erythrocytes in the bone marrow. The active principle is therefore lost through the kidneys.

All indications are that this macrocytic anemia does not develop for a period of two to five years following resection of the stomach. It is also thought that the reserve supply of the active principle is consumed more rapidly in the elderly patient and in those with an active infection. The anemia develops more quickly in such patients.

The authors are to be congratulated. Students of this subject will be well repaid by a careful reading of the original article.

B. B. Vincent Lyon, Philadelphia,
Augustus A. Hall, Columbus, O.

BAKER, W. P.

Metabolism in Gastro-enterology.
J. Am. Inst. Homoeopathy, Vol.
31, p. 664, Nov., 1938.

Possibly endocrine syndromes and gastro-intestinal disturbances are interrelated or confused with one another. For example, in Grave's disease nausea, vomiting, distension, anorexia, often precede the gastro-intestinal crisis while in myxedema marked constipation is a symptom. Baker believes that a knowledge of basal metabolism of patient with gastro-intestinal disorders is very desirable.

M. H. F. Friedman, Detroit.

ALLEN, ARTHUR W. AND WELCH,
CLAUDE E.

Peptic Ulcer Considered From a
Surgical Point of View. New
England Jour. of Med., Vol. 220,
No. 3, Jan. 19, 1939.

The recent influx into the literature of papers concerned with the surgical treatment of peptic ulcer is definite evidence of the discontent with the previously accepted concepts of the treatment of ulcer. The indications for operation are now classified according to the following:

- (1) acute perforation
- (2) cicatricial obstruction

- (3) profuse bleeding
- (4) pain intractable to medical treatment

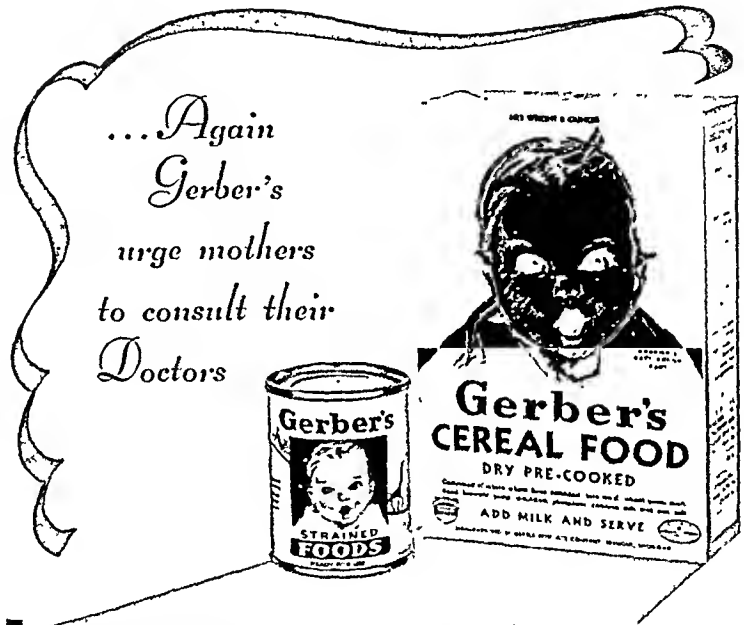
During the past twenty years, the indication for surgery in the latter instance has diminished by about 50 per cent. On the other hand, the indications for operation on the bleeding peptic ulcer patient has become wider in scope.

In the case of acute perforation, early surgical intervention is always indicated, even though the possibility of the walling off of the ulcer by omentum exists. The procedure of choice is simple closure of the perforation; a more radical procedure is unjustifiable because of the increased hazard.

With cicatricial obstruction, where it is difficult to differentiate from obstruction due to edema, an attempt should be made to distinguish between them because of the different methods of handling.

In case of obstruction due to simple edema, operation is contraindicated; medical handling should first be tried. If, however, it cannot be avoided, gastro-duodenostomy is the procedure to be used, bearing in mind that a subtotal gastrectomy can safely be performed at a later date. However, if the obstruction is due to scar tissue, gastro-enterostomy usually affords complete relief.

In instances of profuse bleeding, there is a definite tendency, based



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upon the work of Finsterer, to advocate early operation in the patient over fifty years of age. The operation should be as extensive as possible and must be performed within forty-eight hours after the hemorrhage. In this group, the mortality risk is but little more than in cases where the operation is one of choice.

That group of patients in whom intractable pain is the indication for operation, Dr. Allen feels have, in the past, been incorrectly treated. He feels that a subtotal gastrectomy, rather than a gastro-enterostomy, with removal of three-fifths of the stomach in accordance with the ideas

of Finsterer, Berg and Lewisohn is the only procedure that gives adequate relief to these patients. Although he gives no long follow-up of cases treated by himself, he feels that even the immediate results are more worth while and promising than the procedure of gastro-enterostomy.

Apparently we are about to enter a new period of treatment wherein the surgeon will be called upon in the case of the bleeding ulcer patient more often than in the past. This potentiality comes on at the same period when the Meulengracht diet for hemorrhaging is also surging to the fore. It appears likely that, be-

tween these two new additions to our armamentarium, the problem of ulcer hemorrhage may be solved.

Henry H. Lerner, Boston.

NEDZEL, A. J.

Experimental Gastric Ulcer (Pitressin Episodes). Arch. Path., 26:5-988, Nov., 1938.

The author refers to the fact that in the literature dealing with clinical, experimental and postmortem observations on the pathogenesis of gastroduodenal ulcers there are many conflicting views, but, with the exception of traumatic agents all the findings point to the same fundamental cause of ulcer formation, namely, local nutritional inefficiency, transient or prolonged. Practically all the ways of producing peptic ulcers experimentally involve the integrity of the local blood supply and lead to nutritional changes in the walls of the stomach and duodenum.

With this fundamental idea of ulcer formation in mind the author presents a detailed study of ulcer formation due to pressor episodes evoked by injections of pitressin, because pitressin causes contraction of small arterioles and capillaries which leads to an anoxemic state in the tissues concerned. In the stomach and duodenum hemorrhages, erosions and ulcers, small and large, may be seen resembling those found in man. Single or repeated injections of pitressin were given intravenously to 62 dogs, in 23 of which (37 per cent) there were found lesions in the stomach and duodenum varying from small erosions to large ulcers. A detailed histologic study of the lesions is narrated. The author believes that it has been shown that vascular interference with local nutrition of the tissues is the primary factor in the cause of these lesions; and that it logically follows that peptic ulcers in man should be regarded as a "local expression of a vascular dysfunction inherent in constitutional types unable to withstand the demands of the organism for adjustment to unusual environmental situations."

N. W. Jones, Portland, Ore.

BARGEN, J. ARNOLD, JACKMAN, RAYMOND J. AND KERR, JACK G.

Studies on the Life Histories of Patients with Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis), with Some Suggestions for Treatment. Ann. Int. Med., Vol. 12, No. 3, pp. 339-352, Sept., 1938.

The authors made a statistical study of the records of 870 patients who had thrombo-ulcerative colitis. They took the records of the patients who had been followed from 7 to 14 years after first observation. All



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their patients presented typical clinical, proctoscopic and roentgenologic signs chronic ulcerative colitis of the streptococcal variety. The authors feel that Buie and Bargen made a specific study of these cases and feel that "thrombo-ulcerative colitis" can be suitably applied to this group of cases. It was found that the predisposing factors and factors affecting relapses of the disease are chiefly the following: upper respiratory infection, disease of childhood, dietary indiscretion, physical and mental fatigue, rectal or abdominal surgical operation, trauma, drastic catharses, foci of infection with

sepsis, exposure, dysentery epidemics, and pregnancy. This disease may begin in an insidious manner. Again, it may come on suddenly, as a violent diarrhea without toxic symptoms, or it may start in a fulminating fashion, associated with marked toxemia, fever and all the concomitants of a severe septic process. The major complications and sequelae of thrombo-ulcerative colitis include polyposis, stricture, perianal abscess-fistula, arthritis, erythema nodosum, pyoderma gangrenosa, perforation, liver abscess, carcinoma, phlebitis, iritis, deafness, splenomegaly, nephritis, psychosis, massive hemorrhage, en-

docarditis and kidney stones. There is no special time of year in which this disease begins but it is of interest to note that more of the cases had their onset in January, February, or July than in the other months of the year. The progress of the invasion from the rectum toward the cecum is indicative of the destructive nature of the disease. This is best observed by the roentgenologist. The mortality associated with this destructive infection emphasizes its serious nature. Surgical intervention in this disease should be limited to complications and sequelae. Some of these demand wisely chosen surgical measures, both from the standpoint of the time of their application and from that of the lesion present. An individual afflicted with thrombo-ulcerative colitis presents a poor surgical risk if a surgical attempt must be made to relieve another intercurrent abdominal pathologic condition. The end results of this infection may be devastating but it may also end in complete relief of all symptoms and signs of the intestinal pathologic change. This happy result occurs frequently enough to make it urgent that a well-ordered regimen be followed without deviation by these patients for months and years.

Franz J. Lust.

SPITZENBERGER, O.

Fornix Ventriculi, its Normal and Pathological Conditions in Roentgenology. Roentgenpraxis, 9, 9, 590, 1937.

The author points out that the fornix ventriculi is still very often neglected during the roentgenological examination. He was able to demonstrate the pathological conditions of this section of the stomach better by full-filling or by areogram than by mucosal diagnostic. The impression of the spleen into the fornix can be demonstrated very often. Tumor masses are very well demonstrated by their contrast with the air in the magenblase. It is important to examine for fornix in the prone and supine position of the patient, for, otherwise, pathology in this section of the stomach might be easily overlooked.

Franz J. Lust.

GERSHON-COHEN, J., SHAY, HARRY AND FELS, SAMUEL S.

Experimental Studies on Gastric Physiology in Man VI. The Relation of Size, Shape and Position of the Stomach to its Acid Secretion. Am. J. Roent. and Radium Therapy, Vol. XL, No. 5, pp. 695-704, Nov., 1938.

The normal stomach has a wide range of position in the normal subject. Its position and form seem



to promote BILIARY DRAINAGE

SPECIFIC MEDICATION

in specific biliary
conditions

Plessner bile salt preparations present specific medication for specific lesions of the hepatobiliary tract.

TAUROCOL (Plessner)

Taurocol is of unusual therapeutic value in mild chronic cholecystitis. Containing bile salts, stomachics, and laxatives, it enhances biliary drainage and stimulates intestinal peristalsis.

TAUROCOL COMP. (Plessner)

Contains pepsin and pancreatin in addition to the ingredients of Taurocol. Indicated when gastric or intestinal indigestion complicates gallbladder disease.

Duochol (Plessner) fulfills every demand of the modern therapeutic approach in chronic cholecystitis, toxic hepatitis stone-free cholangitis, and as an aid in the prevention of gallstones in cholelithic involvement. Its combination of highly purified bile salts with sodium salicylate increases the flow of bile from the liver, and improves gallbladder emptying, in this manner promoting biliary tree drainage with its beneficial therapeutic influence.

The reasonable price of Duochol (Plessner) makes it particularly advantageous in the many cases where prolonged administration or frequently repeated courses of therapy are required.

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From *The Seasons* after Richard Westall, R.A., by Charles Heath



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No matter what the season, you probably find it necessary to prescribe additional vitamins for some patients. Making certain that your orders are scrupulously followed, however, is more difficult in spring and summer than at other times. Soaring temperatures may make your most conscientious patients refuse to take bulky, distasteful preparations.

Even finicky patients, however, will take Abbott's Haliver Oil with Viosterol capsules without objection. They are small, soft and tasteless. In addition, since each capsule represents but little more than two calories, they may be administered at any season of

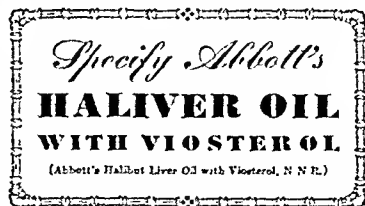
the year without discomfort to the patient or interference with the prescribed diet.

Abbott's Haliver Oil with Viosterol is biologically standardized under rigidly controlled conditions. Each capsule contains not less than 8500 U.S.P. units of vitamin A, equivalent to four teaspoonfuls of cod liver oil of minimum U.S.P. strength, and at least 1700 U.S.P. units of vitamin D, equivalent to ten drops of viosterol in oil.

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with special droppers. To make certain that your patients always obtain a product of proved vitamin potency, it is urged that all your vitamin prescriptions be written.

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conditioned principally on habitus, weight, posture and fullness of the abdominal cavity. The lower border of the stomach has a tendency to become lower with increasing age and probably to a greater degree in females. Achlorhydria seems to be more commonly associated with the steer horn shape of stomach in which evacuation occurs more rapidly than normal. Hyperchlorhydria tends to be more usually associated with the J-shaped stomach and with more rapid motility than with normal acid response in a J-shaped stomach. There seems to be a progressive increase in the number of achlorhydries

and hyperchlorhydries with increasing age and achlorhydria tends to appear later than hyperchlorhydria. No significant sex difference was found in this respect, although in the fourth and fifth decades, women with achlorhydria seemed to predominate, while in the two succeeding decades, men predominated. Hyperchlorhydria seemed to occur most frequently in the third and fourth decades, and earlier in men than in women. The higher the stomach and the more inclined to the steer horn form, the more likely was the habitus to the asthenic and the subject overweight. Achlorhydria was found more fre-

quently associated with the steer horn shaped than with the J-shaped stomach and this association warrants more intensive study in seeking an explanation for the determinants of gastric acid response, the action of the pylorus and gastric emptying time. The position of the patient did not materially affect either the gastric acid response or the emptying time of a given test meal.

Franz J. Lust.

WAHREN, H.

Über die Einwirkung der Aufblähung des Magens auf den Kreislauf. Acta Chirurgica Scandinavica, Vol. 81, p. 43, 1933.

Experiments were performed on rabbits and cats under urethane anesthesia. During the dilatation of the stomach with air there occurred a definite reduction in the minute-volume, the volume of circulating corpuscles and the plasma volume. The blood-pressure, however, remained constant. After administration of lumbar anaesthesia (5% novocaine) the fall in blood plasma volume was arrested. The author discusses the probable reason for this (block of reflex pathway) and compares the experimental results with clinical observations.

M. H. F. Friedman, Detroit.

KIRK, ESBEN.

The Condition of the Tongue in Dehydration and Intestinal Motor Paralysis. Acta Chirurgica Scandinavica, Vol. 81, p. 1, 1933.

Pre- and post-operative observations were made on patients suffering from abdominal conditions requiring surgical intervention. A definite relation was found to exist between the appearance of the tongue and the state of intestinal activity. The tongue was moist in 84% of the cases presenting normal intestinal motor activity and dry in 86% of the patients suffering from motor paralysis but normal in patients with mechanical obstruction. The tongue condition is not related to plasma chloride concentration or to the degree of dehydration.

M. H. F. Friedman, Detroit.

MOORE, L. A., HALLMAN, E. T. AND SHOLL, L. B.

Cardiovascular and Other Lesions in Calves Fed Diets Low in Magnesium. Arch. Path., Vol. 26, No. 4, p. 820, Oct., 1933.

From the Sections of Animal Husbandry and Animal Pathology of the Michigan Agricultural Experiment Station, the above authors report their studies on the influence of diets low in magnesium on the cardiovascular system in calves. When the plasma magnesium was reduced to a low level

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... plus All Enzymes, known and unknown factors of BREWERS YEAST (no live cells).

(*) Proven Therapy in Gastro-Intestinal Dysfunction. Drs. Dougherty, et al. Jour. Dig. Dis., June, 1938.
Relation of Vitamins to Enzymes. J. A. M. A., July 2, 1938.



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In summer months bananas are shipped to far northern points—even beyond the Arctic Circle.

INTERESTING BANANA FACTS

THE ADDITION of ripe mashed banana to the baby's diet contributes not only easily assimilable fruit sugars, vitamins and minerals, but often improves appetite. Ripe mashed banana, fed separately from the milk formula, has been used for the past seven years in a noted foundling hospital as the first solid food for babies six weeks of age and older. As a matter of fact, an increasing number of doctors are using ripe banana in the milk formulas of infants for part or all of the added carbohydrates. The exact amount of ripe banana fed daily varies with the age and strength of the baby.

The key to the varied usefulness of the banana is to be found in its composition. Special points stand out as qualifying it for inclusion in special types of diets. These are summarized in outline form below:

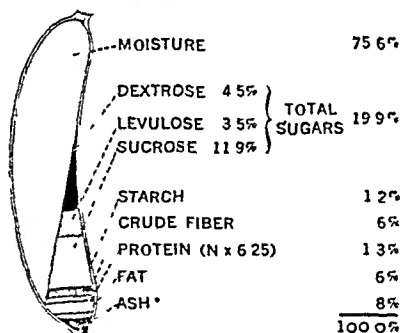
PROPERTIES OF RIPE BANANA PULP

Readily assimilated sugars (along with vitamins, minerals and fiber)
Caloric value (along with vitamins and minerals)
Satiety value and low fat (along with vitamins and minerals)
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Malnutrition
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Preventing Deficiency Diseases
Intestinal Disturbances
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PROXIMATE COMPOSITION RIPE BANANA PULP



*Contains important minerals including calcium, copper, iron and phosphorus

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B-4 to 5	
C-57	

LITERATURE ON REQUEST

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there appeared calcification of the yellow elastic tissue of the blood vascular system, the surfaces of the diaphragm, of the spleen and of the trabeculae of the spleen. The first changes seemed to take place in the endocardium and extend through the larger arteries and veins. In the aorta there was observed fragmentation and degeneration of the yellow elastic fibres. In some cases there was considerable fibro-elastic reaction in the endocardium and in the intima of the larger arteries. This reaction took place around the areas of calcification, indicating a chronic type of irritation. It was not seen in the media or adventitia of the aorta and other larger

arteries, nor was it noted in any other sites of calcification of the yellow elastic fibres. There was also calcification and degeneration of the Purkinje fibres in some of the calves, which, the authors thought, was probably a direct result of the deficiency of magnesium. They suggest the possible relationship of such dietary deficiency to the occurrence of arteriosclerosis in man.

It is stated that from 8 to 10 mg. of magnesium per pound of body weight is required to maintain normal levels of plasma magnesium in some animals, and they quote the figures of 6 to 13 mg. of magnesium intake per kilogram of body weight as being

necessary for children. The average diet of man, unless it contains whole cereals and beans, usually falls below this amount. The suggestion that arteriosclerosis in man may be related to such dietary deficiency is advanced primarily to stimulate further study of the human problem.

N. W. Jones, Portland, Ore.

DOBBS, R. H.

The Treatment of Pyloric Stenosis with Eumydrin. Lancet, Vol. 236, p. 12, Jan. 7, 1939.

A review of the literature shows that of 658 cases of pyloric stenosis treated surgically, 99 died. The greatest cause of death was dehydration and alkalosis, next came gastroenteritis and respiratory infections, while the smallest factor was truly surgical (hemorrhage, peritonitis, sepsis, etc.). As contrasted with this mortality rate of 15%, Dobbs finds in the literature that medical treatment of 93 cases with eumydrin (atropine methylnitrate) showed only a mortality of 5%.

Dobbs presents a series of 20 infants with pyloric stenosis treated with eumydrin. Diagnosis was made on a typical history, visible peristalsis, and a palpable pyloric tumor. 16 cases were cured, 3 were operated on successfully after eumydrin failed, and 1 died during treatment.

M. H. F. Friedman, Detroit.

SEYMOUR, W. B., SPIES, T. D. AND PAYNE, W.

The Gastric Secretion in Chronic Alcoholic Addiction. J. Clin. Invest., Vol. 18, p. 15, Jan., 1939.

A study was made on 40 male alcoholics, all of whom had been drinking heavily for 7 to 40 years. In 71% of the cases the fasting residuum was 20 cc. or less, thick and ropy. After histamine the volume of juice secreted was increased but the response was far below the normal. Fifteen of the men were truly achlorhydric and 25 responded to histamine but the acidity was low. After these results are compared with others, it is concluded that achlorhydria is more frequent in alcoholics with polynuritis than in uncomplicated alcoholics.

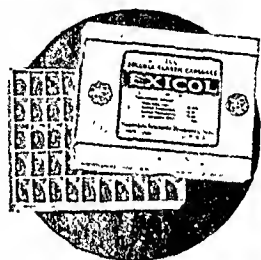
M. H. F. Friedman, Detroit.

DACK, G. M., JOHNSON, R. AND DRAGSTEDT, L. R.

The Effect of Normal and Raw Apple Diet on the Flora of the Duodenum, Ileum and Cecum of Monkeys. J. Inf. Dis., Vol. 64, No. 1, pp. 52-58, Jan.-Feb., 1939.

Raw apple diets have been advocated in the treatment of bacillary dysentery and diarrhea. The monkey was used for study because it is a natural host for bacillary dysentery.

Choosing a Happy Medium . . .



EXICOL

(Oleic Acid and Bile Salts)

The most recent researches* again emphasize the marked fat-intolerance displayed by patients suffering from gall bladder disease, and the satisfactory therapeutic results on a low fat diet and bile salts. Contrary to recent advocates of high fat therapy, it is pointed out that overstimulation of the gall bladder, produced by such high fat diets is undesirable.

Exicol, containing a small quantity of fatty acid and bile salts, offers a solution to the controversial problem of biliary tract therapy. It is the most rational therapeutic agent in biliary disorders because —

1. It stimulates mild gall bladder contractions due to the fatty acid.
2. Increases bile secretion from 100 to 200% ** due to synergistic action of oleic acid and bile salts.
3. Makes high fat diets unnecessary.
4. Exicol is most effective as an aid in the treatment of chronic cholecystitis, biliary insufficiency and other non-surgical as well as post-surgical biliary tract disorders.

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Supplied in boxes of 36 and 100.

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70 Fifth Ave. New York, N. Y.

*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

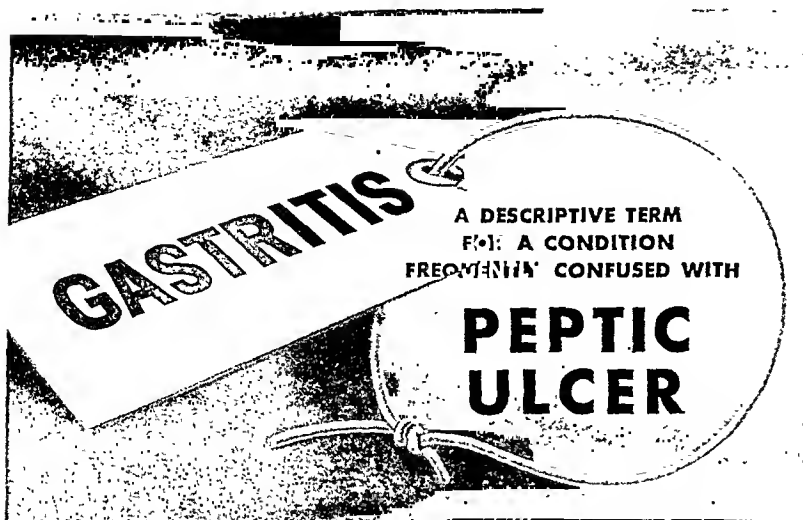


Every doctor has patients whose philosophy of life is "Eat, Drink, and Be Merry". The second part of this quotation, "For Tomorrow We Die", is rarely accorded even a moment's thought by those who enjoy what they call "good living." That is why it is difficult to enforce a sensible regimen in the management of patients whose pathological conditions are due to indiscretions in eating and drinking. One order, however, which most patients will gladly obey is to drink Vichy-Célestins, and many physicians have found this mildly alkaline natural mineral water a useful adjuvant to their regular therapy. We suggest that you order a glassful morning and night in cases of hepatic, biliary, gastrointestinal, urogenital, and metabolic upsets. Vichy-Célestins has a delightfully pleasant sparkle, although it is not heavily charged with CO₂. It promotes secretion and fluidity of bile, favors normal pH of the blood, and is not a laxative. For further information about Vichy-Célestins please write to AMERICAN AGENCY FOR FRENCH VICHY, INC., 285 MADISON AVENUE, NEW YORK, N. Y.

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FABER: GASTRITIS AND ITS CONSEQUENCES.

THE INTRODUCTION of the gastroscope has shown that gastritis, a condition frequently confused with peptic ulcer and even gastric neuroses, is a clinical entity of much more frequent occurrence than formerly supposed.

Whatever the diagnosis, whether peptic ulcer, chronic gastritis, atrophic or hypertrophic, or ulcerative gastritis, the characteristic syndrome is similar and calls for essentially identical treatment.

CREAMALIN, a distinctive colloidal cream of aluminum hydroxide, meets the needs of non-alkaline, antacid therapy in these conditions in an effective way.

A Profound Antacid. Fixes 12 times its volume of N/10 HCl in less than 30 minutes.

Sustained Effect. Unlike the alkalis, its antacid action is prolonged.

No Secondary Rise in HCl. No vitiating secondary rise of HCl secretion is provoked, as is the case with the soluble alkalis.

No Alkalosis. Cannot cause alkalosis or changes in plasma pH.

Quick Healing. Healing is frequently seen in 7 to 10 days by the drip method and 3 to 6 weeks by divided oral doses.

Prompt Pain Relief. Usually affords relief with the first dose.

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THE MODERN NON-ALKALINE THERAPY

for Peptic Ulcer, Chronic Gastritis, Gastric-Hyperacidity



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Fistulae were produced surgically in the duodenum, ileum and cecum of three *Macaeca mulata*. Bacteriologic examinations were made of the fistula contents, especially the relative numbers of *Bact. coli*, the predominating organisms, and the numbers of *Laetobacillus acidophilus*.

pH was not notably changed by the apple diet. *Bact. coli* was usually found in small numbers in the duodenum, increasing in the ileum and cecum. The number was not altered by the apple diet. *Acidophilus* organisms were more numerous in the control period than when the apple diet was given.

Attempts to produce experimental bacillary dysentery were unsuccessful, the animals were probably resistant.

Other authors suggested the effects of apple diet were due to increase in organic acids, partial starvation with rest, or a mechanical cleansing action from increase of bulk and absorption. The latter effect is most likely.

K. W. Benson.

BOARDMAN, W. W.

Acute Infections Gastro-Enteritis. Am. J. Med. Sci., 196, 833, Dec., 1938.

Acute gastro-enteritis, "stomach flu," is very common. A typical epidemic recently occurred in the San Francisco Bay area and was characterized by acute sudden nausea, eramping, watery stools, occasional vomiting, and fever and malaise. It was usually mild and of short duration. In 28 cases among nurses there was no characteristic blood count, in 10 of 15 cases stool cultures showed members of the typhoid dysentery group but no definite classification was possible. Since the organisms didn't agglutinate with the patients' sera the etiology can be called indeterminate.

In institutional outbreaks one must be suspicious of connection between water and sewage lines. Any plumbing fixture where the intake pipe comes directly from the supply pipe and enters below the highest level of the container may act as a siphon if the pressure in the supply pipe falls. The flush valve type of toilet is particularly dangerous. A college physician found that the usual epidemics of diarrhea disappeared after vacuum breakers were put on all flush toilets.

Too little is known about acute gastro-enteritis.

K. W. Benson.

LAHEY, FRANK H.

Experience with Gastrectomy, Total and Partial. New England J. of Med., 220, No. 8, pp. 315-320, Feb. 23, 1939.

Subtotal gastrectomy for ulcer usually results in lower gastric acidity, fewer recurrent ulcers, and a better

LOW COST...plus



Ease of Administration

THE USE of Navitol is distinctly advantageous because it is economical and convenient and provides *natural* Vitamins A and D in highly potent form.

Navitol may be given either in drop dosage or in capsules. The average daily prophylactic dose of 10 drops or one 3-minim capsule supplies 9400 units of *natural* Vitamin A and 1700 units of *natural* Vitamin D (U. S. P. XI).

A blend of specially selected and refined fish liver oils—Navitol costs only about half as much as halibut liver oil with viosterol, yet it has the same high Vitamin D content and an even greater Vitamin A potency. When purchased in 50-cc. dropper bottles, the average dose of 10 drops costs less than a cent a day.

Navitol is supplied in 10-cc. and 50-cc. bottles. Navitol Capsules are available in boxes of 25, 100, and 250. Navitol is widely used both in drop dosage and in capsule form as a routine diet supplement for infants, expectant and nursing mothers, older children, adults and convalescents.

*For literature address the Professional Service
Department, 745 Fifth Avenue, New York, N. Y.*

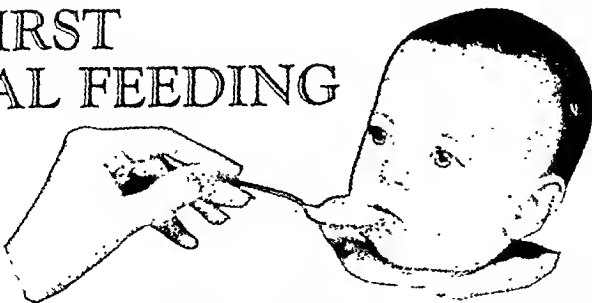
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VITAMIN OIL**

HIS FIRST CEREAL FEEDING

The baby's first solid food always excites the parents' interest. Will he cry? Will he spit it up? Will he try to swallow the spoon? Far more important than the child's "cute" reactions is the fact that figuratively and physiologically this little fellow is just beginning to eat like a man.



PABLUM is now being fed to infants as early as the third or fourth month because it gets the baby accustomed to taking food from a spoon, but, more important, Pablum early adds essential accessory food substances to the diet. Among these are vitamins B, and G and calcium and, equally essential, iron. Soon after a child is born its early store of iron rapidly diminishes and, as milk is poor in iron, the loss is not replenished by the usual bottle-formula. Pablum, therefore, fills a long-felt need, for it is so well tolerated that it can be fed even to the three-weeks'-old infant with pyloric stenosis, and yet is richer than fruits, eggs, meats, and vegetables in iron. Even more significant, Pablum has succeeded in raising the hemoglobin of infants in certain cases where an iron-rich vegetable failed. Pablum is an ideal "first solid food." Mothers appreciate the convenience of Pablum as it needs no cooking. Even a tablespoonful can be prepared simply by adding milk or water of any temperature.

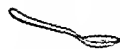
Pablum consists of wheatmeal (farina), oatmeal, wheat embryo, cornmeal, beef bone, alfalfa leaf, brewers' yeast, sodium chloride, and reduced iron.

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Promotes Peristalsis by Bulk and Lubrication

KONSYL OFTEN NORMALIZES LOOSE BOWEL MOVEMENTS

In many cases of looseness of the bowel, especially of nervous origin, Konsyl is the regulating factor.



A Teaspoonful makes a Tumblerful of "Jelly"



Konsyl, the original concentrated vegetable muciloid made from *Plantago Ovata*, by absorbing water and swelling into a soft bland bulk, absorbs excessive intestinal fluids and changes loose movements into even formed stools.

Konsyl is non-irritating, non-habit forming, does not cause leakage and is inexpensive.

Write for clinical test sample and literature.

Also manufacturers of L. A. FORMULA containing Lactose, Dextrin and *Plantago Ovata* Concentrate.

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digestive state than less radical surgical procedures. Subtotal and total gastrectomy offers prolongation of life and possible cure in many cases of carcinoma of the stomach. 8% of duodenal ulcers and 23% of gastric ulcers in this clinic have been treated surgically.

In recent years the mortality of subtotal gastrectomy at the Lahey Clinic has fallen notably, three and one-half years ago it was 18%, the following year 11%, forty-seven cases were done in the last eighteen months without a death.

Satisfactory anesthesia is very important, one to fifteen hundred nupercaine is used in doses up to twenty cubic centimeters, giving complete motor relaxation with little drop in blood pressure.

The Billroth I procedure has been abandoned except for pyloric carcinomas in poor risks. Though it is the safest procedure it is often inadequate and there have been recurrent ulcers in the suture lines.

The Hofmeister antecolic type of resection removing three-fourths to four-fifths of the stomach has proved to be the most satisfactory. Enterenterostomy has been eliminated as it increases risk and it is physiologically undesirable.

K. W. Benson.

LEVIN, M.

Periodic Somnolence and Morbid Hunger: A New Syndrome.
Brain, 59:494, Dec., 1936.

Levin collected seven cases from the literature of what might be called periodic somnolence and hunger. There were attacks lasting several days or weeks in which the patient was abnormally sleepy and hungry. At times there was also some unrest and irritability, incoherent speech, forgetfulness, difficulty in thinking, and hallucinations. Between attacks the patient felt well. The mechanism behind the disease was not clear.

W. C. Alvarez, Rochester, Minn.

OJETTI, F.

Hypochromic Anemia After Gastric Resection in Gastro-Duodenal Ulcer. *Arch. Ital. d. mal. d. app. diges.*, 7:454, Sept., 1938.

Ojetti has studied the gastric juice and blood picture of a group of 81 patients, one to eighteen years after they had been operated upon for gastro-duodenal ulcers. Fifty-one cases had had ample resection of the Polya-Finsterer type and all showed anaehlorhydria. Six cases had had moderate resections and 24 had had conservative operations. The majority of these showed a decrease in the gastric acidity. Nine patients who had had ample resection and 7 who had had a conservative operation re-

In Diarrhea, Colitis, Intestinal Toxemia



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Unlike ordinary kaolin preparations, Patch's Kaolin and Mineral Oil is pleasant to take, is very finely divided, has a high adsorptive power, does not coalesce, and does not produce a secondary constipation.

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Mineral Oil	40%
in a pleasantly flavored Irish Moss Emulsion	

Dosage

1 tablespoonful three times a day, one hour after meals, or as directed by the physician to suit the need of the patient

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An Aid To Normal Bowel Function **KARAJEL**

It's KARAYA GUM processed to permit the formation of smooth, moisture retaining jelly-like bulk in the intestinal tract.

Its bland bulk mixes with food residue to produce pliable, well-formed stools, easy to evacuate.

Its absorption and retention of moisture develops a lubricative, non-irritating bulk that induces normal peristalsis without irritating cathartics.

KARAJEL is prepared in four types: Plain; with Belladonna; with Belladonna and Phenobarbital; with Thiamin Chloride, (Vitamin B-1).

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Neutralizes HCl without alkalizing stomach contents. In peptic ulcer treatment Tri-Calsate may be added to the milk and cream to great advantage. Non-toxic . . . non-irritating. On R in 4½ and 18 oz. bottles.

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vealed either a recurrence of ulcer or bloody stools, and therefore were excluded from the group observed. Out of 42 ample resections, 8 patients revealed essential hypochromic anemia with hemoglobin values less than 80 per cent, and a red count of less than 4,000,000. Of the patients with moderate resection, 6 showed moderate anemia. In 17 cases on whom conservative surgical procedures were done, no anemia was found.

M. R. Berry.

TANNENBERG, JOHN.

Pathological Changes in the Heart, Skeletal Musculature and Liver in Rabbits Treated with Insulin in Shock Dosage. Am. J. Path., XV, 1:86, p. 25, Jan., 1929.

The author reports the changes found in the heart, skeletal muscles and liver of rabbits subjected to various doses of insulin. Twenty-nine rabbits in 4 series were treated with various doses of insulin units per kilo of body weight.

In resume it may be stated that repeated shock doses of insulin produced hydropic changes in the cardiac and skeletal musculature even when no conclusions occurred. The posterior wall of the left ventricle and its papillary muscle showed the greatest alterations, but the lesions were as a rule reversible. At times they progressed to necrosis of small patches of cardiac muscle cells. In the iliopsoas and thigh muscles irreversible changes were more frequent. Single muscle fibres showed lesions varying from fresh breaks to healed and calcified fibres. These changes were considered evidence of the necessity of carbohydrates for the working muscles of the body; indispensable for certain phases of the anaerobic metabolism.

Two types of liver reaction to insulin were observed independent of the size of the doses. (1) The liver gradually released all glycogen synthesized and the blood sugar level was fairly well maintained with the result that convulsions and severe damage to brain and heart were avoided for relatively long periods of time in spite of the repeated administration of high doses of insulin on consecutive days. The rabbits died when all glycogen available was exhausted. (2) More frequently the liver locked up all carbohydrate available as glycogen in the centres of the lobules which constricted by pressure their capillaries; thus, while large amounts of glycogen were stored in the liver, the blood sugar dropped to vanishing levels and convulsions with damage to the brain and heart occurred. The glycogen storage in the liver was considered to be the effect of insulin and other hormones of

antagonistic or synergistic effect on the carbohydrate metabolism produced by the adrenal gland and the anterior and posterior lobes of the pituitary. Simultaneous vascular effects of these hormones were considered essential to produce these changes.

Small areas of focal necrosis were also observed in the livers of rabbits given excessively high doses of insulin.

N. W. Jones, Portland, Ore.

LIUM, ROLF AND PORTER, JOSEPH E.

Observations on the Etiology of Ulcerative Colitis. III. The Distribution of Lesions and its Possible Significance. Am. J. Path., XV, 1:86, p. 73, Jan., 1929.

The authors refer first to the observation of Virchow in 1853 that the distribution of the lesions in ulcerative colitis followed the projections of the mucous membrane caused by the distribution of the muscle tissue lying beneath them.

With this observation of Virchow's in mind the authors studied 6 cases of ulcerative colitis coming to autopsy at the Mallory Institute of the Boston City Hospital. Although the lesions in the 6 cases varied in extent they all showed this muscular pattern. The bases of the ulcers were made up of the circular muscle fibres, and in most cases there was undermining of the epithelial edges. When the fat and mesenteric attachments were dissected away from the muscular layers of the intestine where this linear arrangement of the ulcers was noted it was found that the lesions lay directly over the tenial bands. This was observed in all 6 cases. There was also noted a striking absence of mucus-containing goblet cells in the mucous membrane of the early acutely involved areas.

From these findings it is suggested with much logic that this distribution of the lesions over the powerful muscles of the colon, and the rectum, especially where the severest lesions occur, may be due to the hypermotility and spasm of these muscles. This possible causative relationship is also supported by the fact that early lesions of ulcerative colitis have been produced in the colons of dogs by hypermotility and spasm of the muscles alone.

N. W. Jones, Portland, Ore.

RAO, M. N.

Histidine and Peptic Ulcer. J. Indian Med. Asso., Vol. 7, p. 519, Calcutta, June, 1938.

Concludes from a study of a small number of patients with peptic ulcer that "histidine cannot be classed as an ulcer cure."

M. H. F. Friedman, Detroit.

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BENNETT, T. IZOD, DOW, JAMES, LANDER, F. P. L. AND WRIGHT, SAMSON.

Severe Hemorrhage From Stomach and Duodenum. Lancet, 2:651-655, Sept. 17, 1938.

The authors studied 122 cases entering the Middlesex Hospital during the past three years with hemorrhage from the stomach or duodenum severe enough to endanger their lives. On the basis of their studies they suggest that (1) "the severity of any case can be judged only when it is known how much blood has been lost and whether the bleeding has ceased temporarily or permanently," and (2) "this information can be obtained only by determination of the blood volume."

The estimation of severity of hemorrhage by hemoglobin determination is valueless in as much as immediately after hemorrhage, before the blood plasma has been restored, the hemoglobin is unaltered, being depressed fully only when the blood volume has been restored. The authors therefore study their cases by estimation of both the total volume of blood plasma and of blood corpuscles. A congo-red test is described for measuring the blood volume.

The patients were divided into three groups: Class I had lost less than 20 per cent of their normal cell volume; Class II, 20-50 per cent; Class III, over 50 per cent. Of the 122 patients, 33 fell into Class I, 32 Class II, and 57 Class III. The fatal hemorrhages occurred in Class III. It was constantly observed that the total blood volume remained low until the cell volume had been restored, that is, the plasma volume does not increase over its normal in order to compensate for the cell volume lost. The fallacy of trying to estimate the amount of blood loss by hemoglobin determination is stressed with several examples.

After hemorrhage the hemoglobin will progressively fall due to replacement of the plasma volume and consequent dilution of the remaining cell volume. The one fact pointing inevitably to the conclusion that the bleeding continues is that the cell volume progressively decreases, irrespective of the plasma volume or hemoglobin

M. R. Berry.

SLEETH, C. K. AND VAN LIERE, E. J.

The Effect of Environmental Temperature on the Emptying Time of the Stomach. Am. J. Physiology, 118 (2) 272-275, 1937.

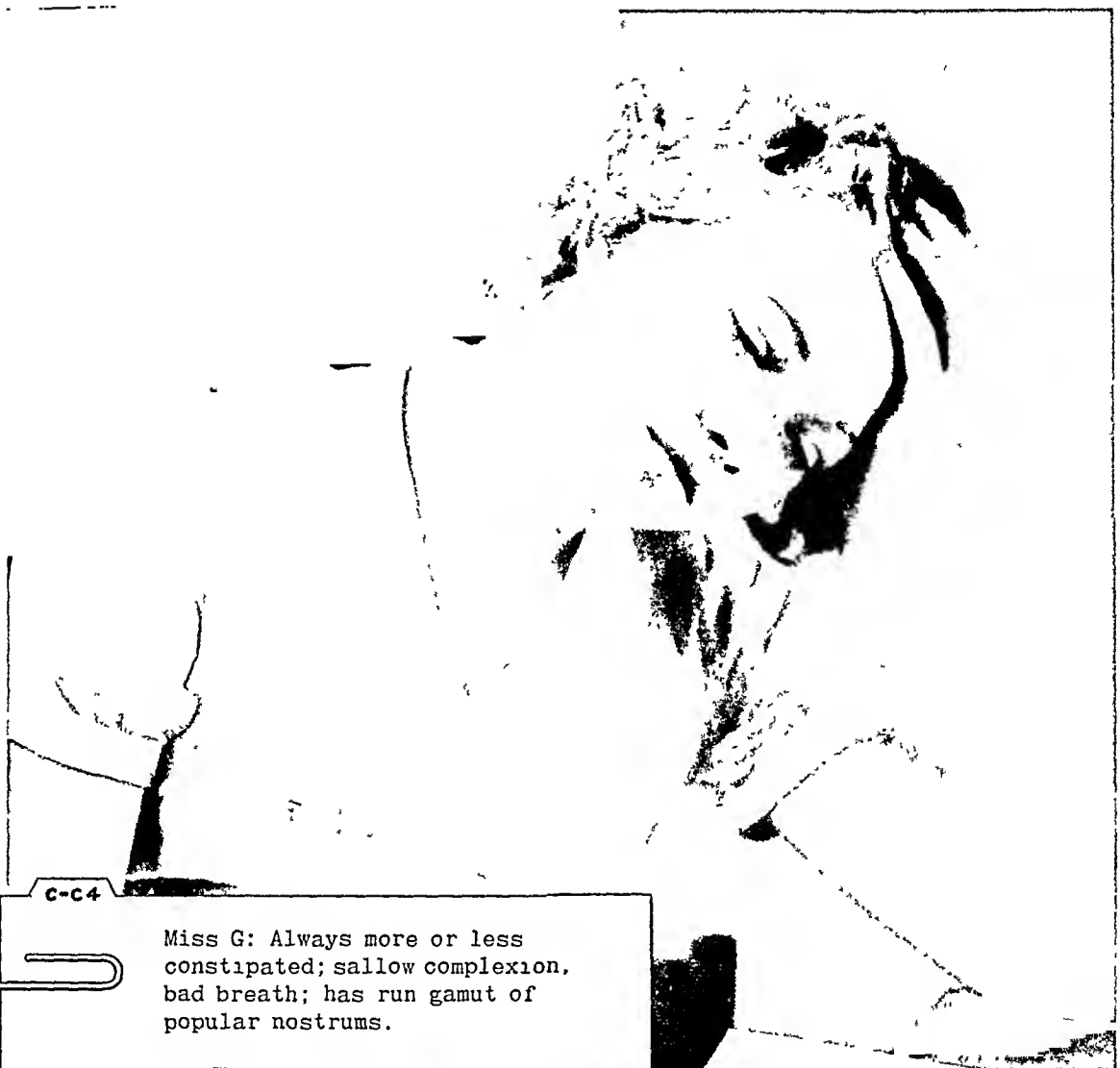
The subjects were five normal dogs, each being fed a standard meal with Barium sulphate, and the emptying time of the stomach noted fluoroscopically at varying environmental temperatures. The authors found that low environmental temperature decreases the emptying time and that high temperatures increase the emptying time. At 15° F. the average decrease was 17% while at 90° F. the average increase was 10%. Thus the individual often feels more hungry during cold weather and less so during hot.

M. R. Berry.

DAM, HENRIK AND GLAVIND, JOHANNES.

The Clotting Power of Human and Mammalian Blood in Relation to Vitamin K. Acta Med. Scand., 96:108-127, Sept. 3, 1938.

The authors summarize a method for the determination of the clotting power of avian blood on addition of tissue extract from the same or related species described by A. Fischer in 1930. The plastic elements of avian blood play a very inferior role in clotting, while in humans the thrombocytes normally play an enormous role. Therefore, a modification of the Fischer method was devised by Dam and Glavind for use with human or mammalian blood. This consisted primarily of the addition of heparin to the plasma in order to prevent clotting before the determination could be made. They express the deviation of clotting power of plasma from the normal by the quotient $R = K/K_n$, K_n being the concentration of tissue extract



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added to normal serum which will produce clotting in three minutes. K is the concentration of tissue extract required to cause clotting of the serum in question in three minutes. R increases therefore as the clotting power decreases, and $R = 1$ in normal serum (0.5 — 2.0).

The fact is verified that tissue extract of the same or related species must be used, and the authors describe a method of preparation of human tissue extract. Storage of the plasma for several hours reduced the clotting power somewhat. Mild K-avitaminosis was induced in one of three rabbits by feeding a diet of ether extracted oats and fresh mangolds supplemented with Vitamins A and D. The R value was determined in the following diseases:

Essential thrombopenia	4 cases	$R = 1, 0.74, 0.65, 0.8$
Aplastic anemia	2 cases	$R = 0.8, 1.0$
Hemophilia	4 cases	$R = 1.3, 1.2, 1.0, 0.7$
Nontropical adult sprue	2 cases	$R = 0.75, 1.4$
Myeloma	1 case	$R = 0.6$
Hepatitis acuta	4 cases	$R = 0.9, 2.2, 2.7, 2.0$
Obstructive jaundice	9 cases	$R = 1.0, 10, 78, 5.6, 5.4, 33, 1.1, 24, 12$

Thus the R value was often high in cases of obstructive jaundice though many of these revealed no clinical signs of a hemorrhagic diathesis. Although the platelet count was considerably reduced in essential thrombopenia and aplastic anemia, the R values were found normal. The normal R value in hemophilia substantiates the hypothesis of Howell and Cékada that the platelets are at fault.

The factors influencing the R value are fibrinogen, calcium, pII, prothrombin and anti-coagulating substances. The authors assume that the level of prothrombin is responsible for the decrease in clotting power since they show that the serum of these cases closely resembles that of K — avitaminous chicks and plasma from which prothrombin has been removed by absorption. The reason

why obstructive jaundice leads to a coagulation deficiency due to reduced prothrombin level which may be restored by Vitamin K is probably the fact that Vitamin K and other fat soluble substances are poorly absorbed from the intestine when bile is absent. The well known fact that the hemorrhagic condition is often developed after operation is probably due to the fact that the quantity of bile acids in the bile is abnormally low during the first weeks after the release of occlusion. It was possible to restore the clotting power to normal in these chicks by a single intracardial injection of a Vitamin K concentrate. In five cases of obstructive jaundice it was possible to restore the clotting power to normal with three to five intramuscular injections of emulsions of Vitamin K.

In normal plasma, prothrombin is present in such large quantities that it may be considerably diluted before the R value increases rapidly. The excess of prothrombin in chicks is so great that it requires about twenty-four days after choledochus ligature to reduce it enough to give high R values. After this, a period of a few days without intestinal bile leads to a rapid increase of the R value. This suggests the pre-operative use of intravenous and intramuscular Vitamin K in cases of obstructive jaundice.

M. R. Berry.

BERMAN, T. M.

Miliary Calcifications in the Spleen. Radiol., 29:37, 1937.

Berman has seen eighteen cases of miliary calcification of the spleen discovered accidentally during the course of X-ray examinations of the chest and abdomen. Fortunately for the cause of science, three of the patients came to necropsy, and then histologic studies showed that in all three cases, the calcifications were due to phleboliths. There were none due to tuberculosis as one might have guessed.

W. C. Alvrez, Rochester, Minn.

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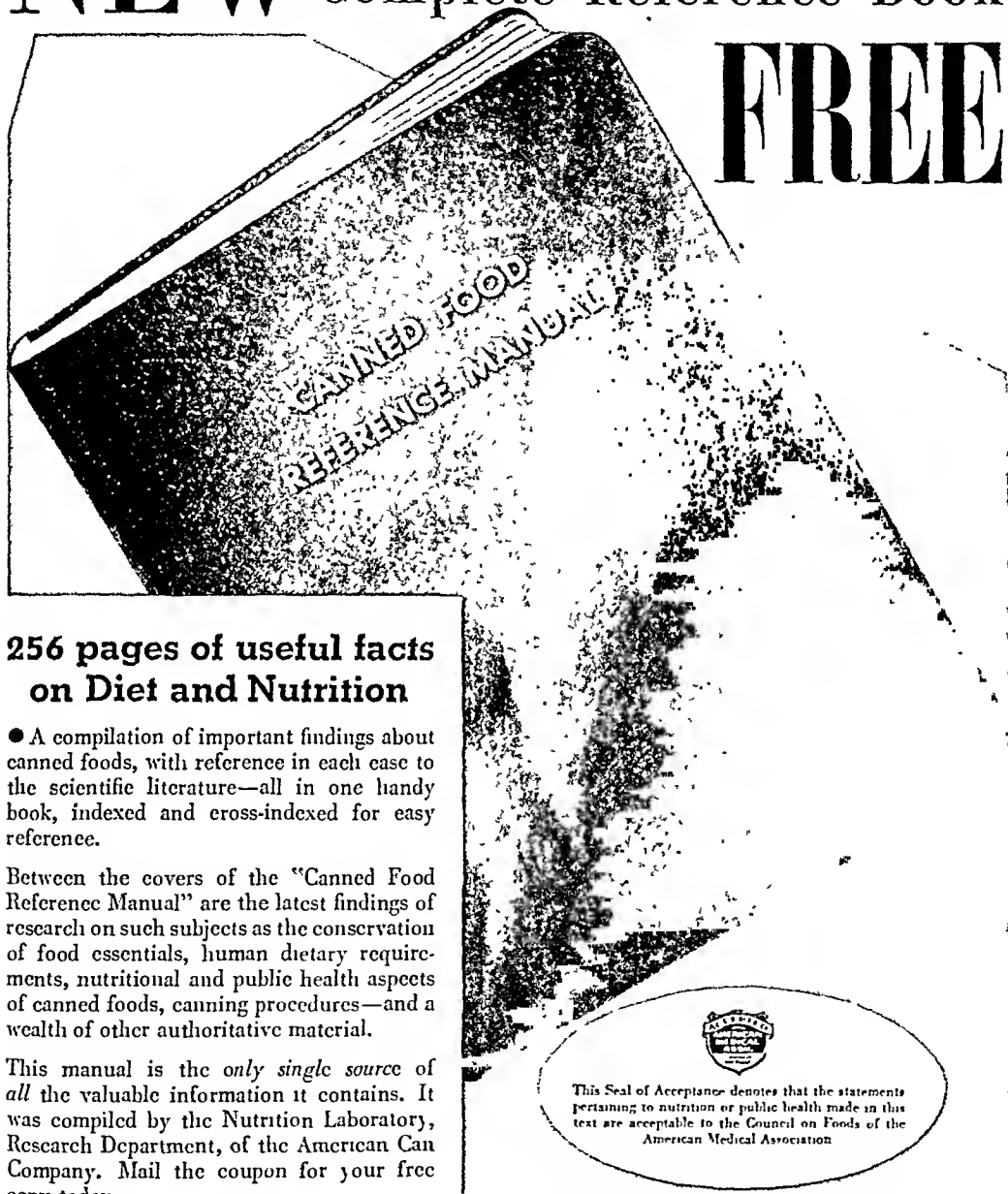
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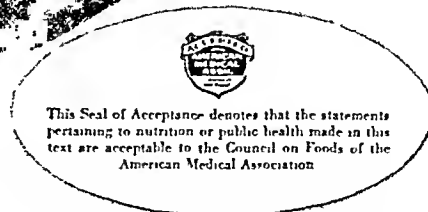


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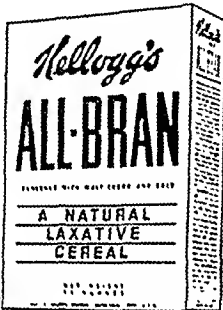
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Contributions Made in 1938 to Knowledge in Regard to the Pancreas

By

ROBERT ELMAN, M.D.

CONSIDERABLE work has been reported during 1938 on the pancreas, most of it continuing along paths previously started. In the past clinicians paid very little attention to the pancreas (aside from the islets of Langerhans which are not considered in this review) because its digestive function was considered relatively unimportant and disturbances in its functions were thought to be rare. Moreover, the pancreas was difficult to palpate, tests of its function were complex, symptoms produced by disease in it were vague, and hence, most physicians relegated it into the limbo of forgotten organs and its lesions into forgotten diseases. This situation has now undergone a definite change owing to several investigative attacks made during the past decade, more particularly during the past few years. In large part these studies have taken two directions, first toward an understanding of acute pancreatitis and second toward an understanding of the role of the pancreas in fat metabolism especially as it affects the liver. In the following brief review of the literature of 1938 only the most significant papers are discussed, or those that the reviewer thought were most important.

Anatomy. Numerous papers have dealt with the anatomic relations of the pancreatic and common ducts. In contrast to most of the older work, recent observations have tended to show that these two ducts form a common channel in a large rather than a small percentage of human subjects. Such an anatomical arrangement is significant in that it may permit pancreatic juice to enter the common duct and gall bladder or conversely, bile to enter the pancreas, events which might induce or promote inflammation or other changes. Of the direct anatomic observations, that of Mehnen (34) is worthy of note. This worker dissected at autopsy 449 specimens and described 4 types of cases. The two ducts joined above a common sphincter in 61% thus permitting reflux of bile or pancreatic juice. This is a much higher figure than the 20% reported by Mann and Giordano in 1923. Mehnen also found that of the 275 cases with a common ampulla 35% had stones in the gall bladder in contrast to 14% in the 174 cases with separate duct openings. These and other findings are, however, of importance in the study of cholecystic rather than of pancreatic disease, in that they support the idea that pancreatic juice may flow back into the biliary tract to induce changes there. Mehnen reported no observations on lesions in the pancreas.

Of greater physiological value are the observations in living patients in whom the pancreatic duct was visualized after injection of radiopaque oil in the common duct, through a T-tube, a procedure not infrequently carried out during the course of biliary operations. The X-ray picture thus procured is called a cholangiogram because the bile duct radicals are

also visualized. These reports have been fairly numerous both in this country and abroad. The names of Bottin (7), Best and Hicken (6), Colp and Doubilet (14) and Leven (28) should be mentioned. The last named observer found such a visualization of the pancreatic duct in 23% of 91 patients who had had 203 cholangiograms. Colp and Doubilet (14) also studied the bile from such patients for pancreatic ferments and found amylase in significant amounts in 28.5% of all cases, thus adding further evidence as to the frequency of reflux of pancreatic juice into the common duct. It is important to state that in nearly all the cases reported, spasm of the ampulla and not a stone was thought to be the factor in producing obstruction and back flow. Cholangiograms have even been obtained during operations on the biliary tract for diagnostic purposes, the most extensive experiences being reported from Sweden by Hulten (23). This author used a radiopaque substance which is water-soluble. This he injected into the cystic duct at operation. He found that in about 10% of his cases the pancreatic duct was visualized.

Pharmacology. A few reports regarding the pharmacology of the pancreas have appeared. McCaughan, Sinner and Sullivan (33) studied a patient with a pancreatic fistula which had followed a gastric resection. The effects of various medicaments as well as foods were observed. The total volume of pancreatic secretion averaged 600 cc. per day. Craft (15) studied the effect of ephedrine in the secretion of pancreatic juice in a number of dogs. The findings indicated a suppression of secretion averaging 31% in 24 hours following the injection of 10 mg. every 2 hours. In this connection it is of interest that Jacquet, at a meeting of the Société médicale des hôpitaux of Paris (24), stated that he had observed in three patients with acute pancreatitis, relief of epigastric pain following the injection of ephedrine after morphine had proved ineffective. The clinical diagnosis was verified by operation in two of the three cases. Gilbert-Dreyfus at the same meeting cited a case exhibiting an edematous pancreas at operation; striking relief of symptoms after operation followed injections of .06 gm. of ephedrine hydrochloride. These reports may have some connection with the observation in this country that nitroglycerin relieves certain cases of "biliary colic" which is explained as due to its effect in relaxing the sphincter of Oddi (Best and Hicken).

Experimentally Produced Disease. The method of experimental production of pancreatic disease has been largely that of excision or ligation of ducts for the purpose of studying digestive and metabolic changes; these will be considered below. Baxter, Baxter and McIntosh (4) have, however, produced acute pancreatitis by injecting bile obtained from the gall bladder into the pancreatic ducts. They then studied the level of serum lipase and found in 7 dogs

a rise which lasted for 24 to 48 hours and then declined gradually to normal in 7 to 10 days.

Acute Pancreatitis. Clinical reports of pancreatic disease have been concerned for the most part with cases of acute pancreatitis, particularly with regard to the question of operative vs. non-operative therapy. Weiner and Tennant (42) presented a statistical study of 40 cases of pancreatic necrosis observed at autopsy, an incidence of 1%. Chronic pancreatitis was more frequent (2.4%). Of some interest is the fact that in half of 51 cases of periportal cirrhosis there were pancreatic lesions, an association which will be mentioned later. They noted that although the incidence of cholecystic lesions in pancreatic disease was increased, the converse was not true. In a large percentage (66%) of their cases of pancreatic necrosis there was an alcoholic history. There was little evidence of duct metaplasia producing obstruction in contrast to the recent findings of Rich.

Cole (12) presented an able review of the modes of treatment of acute pancreatitis which summarized the present status of the problem. Though there is general agreement that conservative therapy should be carried out in acute edematous pancreatitis, confusion still exists in regard to acute pancreatic necrosis. An obvious problem is that of knowing which of the two types is present in a given case. Cole expresses his point of view by favoring operation when the diagnosis is uncertain, when signs of peritonitis are present, or when an abscess has formed. He is inclined toward conservative therapy when the diagnosis is certain, when collapse is severe, or when the inflammatory process is confined to the retroperitoneal tissue.

The tendency against early operation in acute pancreatitis has been expressed by Abell (1) who analyzed his experience in 30 cases, all operated on at once with a total mortality of 30%. It is important to note that acute edema of the pancreas was present in 9, whereas the rest showed necrosis, hemorrhage or abscess. The deaths all occurred in the latter groups. This author believes that the various lesions are stages in the same disease. In Germany a recent report by Kufferath and Volkmann (26) cites 65 cases. In 28 the patient was subjected to immediate operation with a mortality of 53%, whereas in 26 cases in which the patient was not operated on the mortality was only 23%. Insufficient data were presented, however, to classify these cases into those with and those without necrosis. Turning to this country again we find an experience with 14 cases described by Dunlop and Hunt (16). All but two were of the hemorrhagic type: all patients were operated on at intervals varying from 7 hours to 16 days after admission. There were only 2 deaths in cases in which the patient was operated on on the 5th and 6th day. These data hardly support the view that operation should be delayed. On the other hand, Walker (41) summarizing 70 cases (with 40 deaths) at the Boston City Hospital, found that those patients operated on with symptoms lasting from 2 to 6 days had the lowest mortality. Hence he advocates moderate delay.

It is obviously impossible to draw any dogmatic conclusions in regard to the question of operation in these cases. Certainly if the mild cases can be recognized the patient can safely be watched; and most observations show that the attack will subside rapidly. Such a group of 21 cases has been described by Gray,

Probstein and Helfetz (18). These authors have designated the disease as Transient Acute Pancreatitis and have fully reviewed the literature. Other synonymous terms are acute interstitial pancreatitis, acute edematous pancreatitis, acute non-hemorrhagic pancreatitis. The value of repeated determinations of the blood amylase in the diagnosis and progress of the disease is emphasized by these authors. Cole (13) has also studied the behavior of blood amylase in 8 cases of acute pancreatitis, 6 of them showing acute edema of the pancreas at operation, and has found it to be valuable diagnostic aid. Loeffler (29) described several cases of transient acute pancreatitis in which a rise and fall of urinary amylase coincided with the height and subsidence of the attack. In one patient 3 successive attacks were observed each accompanied by a spike in the output of diastase in the urine.

If one excludes such mild or transient cases and considers only the severe lesions associated with hemorrhage and necrosis, the problem of operation assumes real importance because of the high mortality in this group regardless of the type of therapy. The present writer is inclined to the view that this group of patients is primarily surgical and that operation for the drainage of the lesser peritoneal cavity should be carried out as soon as the diagnosis is made and the patient becomes operable. Certainly it should be emphasized that in the study of acute pancreatitis a clear differentiation be made whenever possible between the pancreas which is merely inflamed and the one which is necrotic (or hemorrhagic).

Carcinoma. Lahey and MacKinnon (27) have reported their experience with 47 cases of carcinoma at the head of the pancreas. They emphasize the fact that jaundice is not always painless, inasmuch as 76% of their patients presented some pain as one of the symptoms. They feel that radiotherapy is of value inasmuch as those receiving it lived 17 months in contrast to 8.6 months for those not receiving it. These authors recommend that an anastomosis be made between the gall bladder and jejunum rather than between gall bladder and stomach or duodenum. A more detailed report of 109 cases of carcinoma of the pancreas verified by operation or autopsy, by Ransom (36), indicates that extreme and rapid loss of weight was the most common symptom. Duration of life after operation averaged 7.2 months. In the face of this hopeless picture the experience reported with total excision of cancer of the pancreas as described in 1935 by A. O. Whipple and his co-workers seems promising, indeed. In a recent paper by Whipple (43) the subject of excision is brought up to date with a description of his present technic.

Pancreatic Insufficiency. Most of the papers on the pancreas in 1938 have dealt with the question of pancreatic insufficiency (i.e. pancreatogenous diarrhea) and especially with the fatty changes in the liver which follow pancreatectomy. In respect to the first topic, a number of clinical studies have appeared on the association of pancreatic lesions with the occurrence of steatorrhea and azotorrhea, i.e., the bulky frequent stools which contain such a large amount of unabsorbed protein and fat. Loeper, Le Maire and Lesobre (30) describe a patient with this type of diarrhea and jaundice who at autopsy showed a cystic atrophied pancreas with almost complete disappearance of acinar tissue. The liver was large. They cited 10 similar cases from the literature in 3 of which the

patients presented no symptoms during life! Roux (38) reported the beneficial results following dietetic and pancreatin therapy in a patient with similar symptoms as well as ascites and edema. The X-ray showed stones in the region of the pancreatic duct and an enlarged liver upon which the anatomical diagnosis was based. Snell and Comfort (39) described 2 cases with hepatic lesions presumably secondary to pancreatic lithiasis and atrophy which will be mentioned below. Hotz (22) discussed the question of steatorrhea from the purely clinical point of view with special reference to its differential diagnosis and therapy. On the basis of his evidence he felt that few of these cases are pancreatogenous, e.g., due to chronic pancreatitis, but are really due to sprue. He emphasized several important differences which seem significant. For example, the fecal excretion of nitrogen is normal in sprue but increased in pancreatic lesions, i.e., steatorrhea is characteristic only of pancreatic insufficiency. He also notes that in the latter condition the sugar tolerance curve is elevated whereas in sprue it is normal. This is the same difference noted by Harper (see below) between pancreatogenous diarrhea of infants and celiac disease.

Of the association of steatorrhea and pancreatic disease the most convincing evidence has appeared in the pediatric literature. Harper (21), for example, reported 8 cases all studied completely with analyses of fecal fat excretion; in the four autopsied cases atrophy of the pancreas was found. Harper emphasizes the differentiation between this type of congenital steatorrhea due to pancreatic defect and so-called celiac disease in which the pancreas is normal. Among other things he finds a low percentage of split fat and a high glucose tolerance curve in the former in contrast to the opposite findings in celiac disease. Thomas and Schlutz (40) described one similar patient with the same chemical and autopsy findings, including the finding of a high per cent of neutral fat in the stool in contrast to the high per cent of fatty acid in celiac disease. The most thorough study, however, is that of Anderson (2) who has analyzed 49 cases in infants and older children, in all of whom an autopsy was done, all showing cystic fibrosis of the pancreas or replacement of acini by adipose tissue. The liver was frequently enlarged and fatty, an association discussed in some detail below. The frequency of pulmonary lesions in these children is noted and the idea suggested that these lesions were secondary to Vitamin A deficiency. She also reported 32 cases of celiac disease; in 11 of them the pancreas was examined microscopically and no lesion found. The discussion of the various problems involved is stimulating and provocative of further work. There have always been a great many problems presented by patients exhibiting so-called pancreatogenous diarrhea (i.e. steatorrhea and azotorrhea). While it is nearly always produced by atrophic disease of the pancreas it may occur without such a lesion. Moreover, adults particularly, may have no digestive or other disturbances and yet harbor a pancreas whose acini are nearly all atrophic. The importance of chemical analysis of the stool in these cases should be emphasized. Of the two substances, fat and protein, the latter is probably the better, first because it is the simplest to measure, requiring but a Kjeldahl determination of the stool, and second, because as pointed out by Thyssen it is a more reliable index in most patients on a mixed diet, especially when

they have been on a low fat regime. The role of absorption of vitamins and perhaps other factors such as lipotropic substances lends complexity to the problems but also furnishes new avenues of approach not only in the extreme cases of pancreatic insufficiency but other conditions in which such a condition is slight or transient.

Pancreas and Liver. Of extreme interest in many of the above reports is the condition of the liver which is often described as large and fatty. Such hepatic deposits of fat have long been noted in depancreatized dogs kept sugar-free with adequate doses of insulin. It was soon discovered that raw pancreas by mouth prevented this deposition of fat. Later Best and others found that choline and lecithin also cured or prevented this abnormal fatty liver. Still more recently Dragstedt has obtained a pancreatic extract which he has named lipocain which has the same lipotropic effect and which he claims is different from either lecithin or choline and is in fact of the nature of a hormone. During 1938, a number of studies appeared dealing with this pancreatic extract. That the fatty liver is of wider interest is suggested by the interesting observation of Chaikoff, Connor and Biskind (9) who have found that the above mentioned fatty changes gradually regress and are replaced by cirrhosis. They found that in 4 dogs, kept from 2.6 to 5.5 years, the livers presented a picture of far-advanced portal cirrhosis with normal fat content and no indication of preceding fatty infiltration. This association of pancreatic insufficiency with cirrhosis of the liver lends considerable practical interest to the following experimental findings. Thus, this work, though primarily concerned with the liver and fat metabolism, because of its connection with pancreatic disease, offers new avenues of research, not only as regards pathogenesis but more particularly as regards therapy.

The existence of a fat-metabolizing substance associated in some way with the pancreas seems clear. Where and how it operates is still a matter of dispute although most work indicates that it is not primarily connected with the digestive ferments produced by the pancreas. The fact that fatty changes followed pancreatectomy but did not result from ligation of the ducts supported the idea of Dragstedt that a hormone was responsible. Boyce and McFetridge (8) confirmed this idea when they found hepatic fat deposits only when all of the pancreas was excised. That the deposits were not due to digestive disturbances was shown by fecal analyses showing no abnormal loss of protein or fat in these experiments. In contrast are the findings of Ralli, Rubin and Present (35) who observed fatty livers indistinguishable from those following pancreatectomy, in 3 dogs whose pancreatic ducts were ligated 13-15 weeks before. Slight steatorrhea and creatorrhea were present in 2 dogs receiving lecithin, and moderate changes in 1 not receiving it. This difference as to the relative changes in digestion produced by pancreatectomy and by ligation of ducts is a well known one. Differences have also been reported in the results of ligation alone, apparently dependent upon occult or uncontrolled factors.

The literature on the effect of experimentally excluding pancreatic juice from the intestine has been summarized by Handelsman (20) who has added some new data. This author suggests that animals without a pancreatic secretion show a labile digestive mechan-

ism good at times and poor at other times. This variability has also been noted by others after pancreatectomy. The present reviewer suggests that this may be correlated with the previous diet of the animal particularly in regard to the degree of storage of vitamins or other food factors in the liver as a result of such previous diets. Chaikoff and Kaplan (10) studied not only the fatty liver following pancreatectomy but also the elevation of blood lipids which also occurs. They note that the pancreatic extract which prevents and cures hepatic deposits of fat is heat-stable whereas that which controls blood lipids is heat-labile. These workers also present observations which are opposed to some of the observations of Dragstedt.

Another series of experimental studies on the relation of the fatty liver to the pancreas concerns the production of the former lesion by the feeding of a high fat, low carbohydrate, low choline diet in the absence of any injury to the pancreas. MacKay and Barnes (32) present evidence which tends to show that lipocaine, the fat-metabolizing extract from the pancreas (Dragstedt), does heal such fatty livers, or perhaps prevents their formation, not because of any specific hormone but because of its content of choline and protein. The data are too detailed to present here but the conclusion reached is that "our experiments support the view that reduction of liver fat by lipocaine is due to the sums of the lipotropic effects of the choline and protein it contains." This point of view is also stated by Best and Ridout (5) who present findings showing that the fat deposits produced by a basal diet in rats are affected primarily by choline and that there is no lipotropic element in lipocaine aside from its content of choline and protein. In contrast, however, are the findings in similar feeding experiments in rats reported by the English workers, Channon, Loach and Tristram (11). They find that pancreatic extracts (lipocaine) have an effect greater than could be attributed to its choline content and that the non-choline activity is not accounted for by the protein content. It must, of course, be realized that these experiments dealt with fatty livers produced by diet, and they may

present an entirely different problem from the lesion produced by pancreatectomy as studied by Dragstedt and other workers.

Turning to clinical studies of fatty livers one finds encouraging reports following the use of pancreatic preparations. Thus Snell and Comfort (39) noted improvement in two cases of hepatic lesions presumably secondary to pancreatic lithiasis and atrophy following the use of lipocaine and pancreatic juice. Borgen, Bollman and Kepler (3) used pancreatic insufficiency with diarrhea, presumably with stentorrhea and creatorrhea, though no fecal analyses were reported. Grayzel and Radwin (19) studied 3 children with diabetic hepatomegaly over a fairly long period and observed striking regression in the size of the liver as well as a fall in blood lipids following the use of pancreatic extract (lipocaine). Adequate control periods were observed. Rosenberg (37) presented a similar experience, in an adult diabetic in which biopsy specimens of the liver before and after treatment were correlated with the improvement in the clinical picture and blood chemical changes.

Roentgenology. Aside from the cholangiograms already discussed, X-ray seems of limited value in the diagnosis of pancreatic disease. Three patients are described by Frostberg (17) who observed characteristic changes in duodenal contour following a barium meal; this author however emphasizes the difficulty in interpreting such changes in terms of pancreatic disease. In large pancreatic tumors and especially in pancreatic cysts a more clear-cut diagnostic picture is obtained, as emphasized by Ludin (31), who also discusses the problem of roentgenological diagnosis of pancreatic disease. He cites the importance of X-ray shadows of pancreatic stones as an important means of diagnosis in this rare condition. A similar experience is related by Kini (25), the X-ray diagnosis of pancreolithiasis being confirmed at operation. Other cases of pancreolithiasis have been reported by Roux (38) and Snell and Comfort (39).

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The Roentgen Diagnosis of Early Enlargement of the Head of the Pancreas

By

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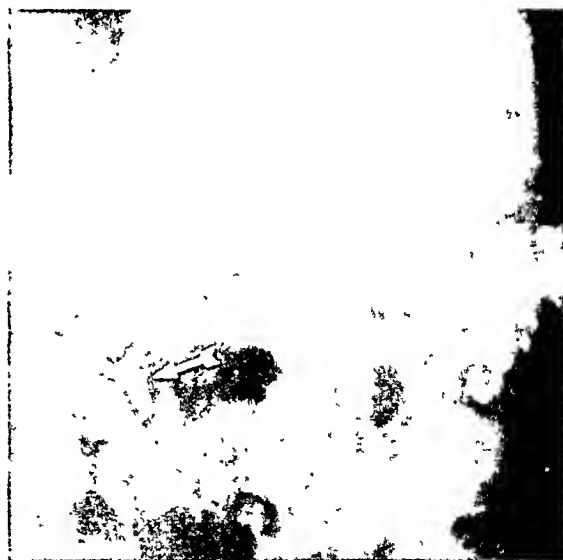
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THE roentgenologic exploration of the pancreas by direct methods has been impossible up to the present time. The roentgen diagnosis of pancreatic disease has been very unsatisfactory and unreliable in many instances. A diagnosis of pancreatic disease is possible only in late instances where an enlargement of the head of the pancreas produces signs of pressure on the adjacent organs. Owing to the anatomic position of the pancreas, its relation to the concave aspect of the duodenum and greater curvature of the prepylorus, pressure defects may be observed in cases with neoplasm or inflammatory process involving the head of the pancreas. Since the majority of lesions of the pancreas usually involve the head, a meticulous mucosal roentgenologic examination should be made with compression in order to recognize the early changes in the ampullary portion of the descending duodenum. Little attention has been directed to the mucosal configuration and contour of the peri-ampullary portion of the duodenum. More recently we made a painstaking study of a small series of cases, paying particular attention to the mucosal configuration of this segment of the duodenum. We have encountered two cases revealing typical roentgen signs, showing evidence of a filling defect, shaped like an inverted three, in the ampullary portion of the duodenum. This defect represented evidence of pressure of the head of the pancreas. The roentgenograms showed two small depressions, of smooth contour, well defined, with a small projection between the depressions which formed the inverted figure three. The configuration of Kirkrings folds is distorted and displaced and the surrounding mucosa show evidence of pressure.

Heretofore the roentgenologist's technique and experience did not permit an early diagnosis of lesions in the second portion of the duodenum until marked changes were demonstrable. However, slight changes in the direction, shape and contour of the mucosal markings now offer a means of early diagnosis of disease of the head of the pancreas which have previously evaded our attention. The roentgenologist need not wait for the marked distention, displacements, pressure defects and stenosis, to make a diagnosis of a lesion of the head of the pancreas. These are late signs which

do not offer any difficulty in diagnosis. Examination of the ampullary portion of the duodenum with special attention to the changes in contour, and changes in mucosal markings will often yield findings of inestimable diagnostic import.

Frostberg recently reported three instances in which he demonstrated a typical roentgen picture in the

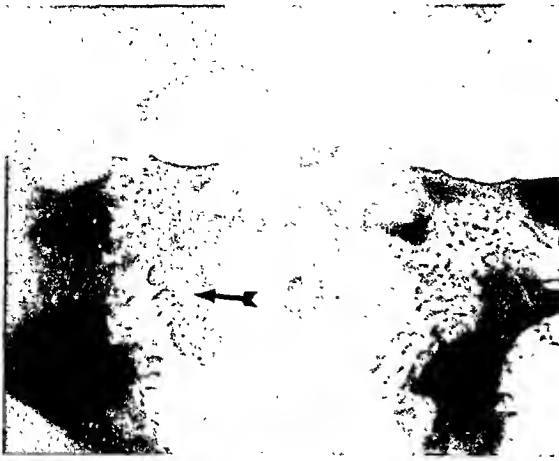


Case 1, Fig. 1. The inverted three filling defect is shown at arrow. Note the compression of the mucosal folds. The two small depressions and the small protrusion between them is demonstrated.

form of an inverted three, which was produced by pressure, due to a slight enlargement of the head of the pancreas. His observations were confirmed by autopsy studies.

A brief report of our two cases with roentgenographic illustrations of the characteristic inverted three deformity is shown in Figs. 1 and 2.

Case 1, male, aged 51, obese, complained of epigastric pains of six months duration, loss of weight, abdominal distention, belching and constipation. A gastro-intestinal



Case 2, Fig. 2. The sharply outlined inverted three pressure defect is shown at arrow. The two small depressions and the protrusion between them is well illustrated. The depressions represent slight pressure of the head of the pancreas. The protrusion the papilla.

X-ray revealed a prepyloric narrowing with mucosal changes suggestive of a gastritis; an inverted three pressure defect on the concave aspect in the ampullary region of the descending duodenum; irritable colon (mucous colitis stringing). A gall bladder visualization test revealed a normal functioning gall bladder, without stones.

Case 2, male, aged 57, complained of vague digestive disturbances, gas, distention, bloating of abdomen, no pain. Examination of stools revealed evidence of a pancreatic disturbance, and also occult blood. A gastro-intestinal X-ray examination showed a rapidly emptying stomach, with a deformity of the duodenal cap due to an ulceration; the descending portion of the duodenum in the ampullary segment showed an inverted three filling defect due to slight pressure as result of enlargement of the head of the pancreas. The remaining small intestine was normal;

colon was markedly irritable. A gall bladder visualization test revealed a normal functioning gall bladder without stones.

SUMMARY

The roentgenologic diagnosis of early changes in the head of the pancreas is presented with a report of two cases. Roentgenologic changes in the mucosal configuration and contour of the ampullary portion of the duodenum now offer a newer field in the diagnosis of intrinsic and extrinsic pathology affecting this segment of the intestine. Since the majority of lesions of the pancreas involve the head, its close relationship with the ampullary portion of the duodenum is more likely to reveal some abnormality of the duodenum. If more attention is focused upon this area the roentgenologic examination should yield changes leading to a correct diagnosis in many instances. It is now possible to demonstrate the finer details in the configuration of Kirkrings folds by the compression method. Minute changes in the mucosal pattern in the ampullary portion of the duodenum have hitherto escaped our attention. The new roentgen sign illustrated by an inverted three defect in the descending duodenum is produced by pressure of the head of the pancreas. The mucosal markings are displaced but not effaced by this pressure. The roentgen sign described as being due to disease of the head of the pancreas, though indicative of pressure does not in itself determine the etiologic factor, as any pathologic process involving the head may produce a similar picture. However the roentgen demonstration of pressure due to slight enlargement of the head of the pancreas aids in localizing the lesion and with further corroboration of the clinical and other laboratory data is of inestimable value in the diagnosis of early pancreatic affections.

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A Roentgenologic Consideration of Colopathies Associated With Gall Bladder Disease

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THE opinion that irritable and other conditions of the colon are frequently associated with gall bladder disease, has been voiced by many authorities. However, there is no unanimity of opinion that gall bladder disease and irritable states of the gastro-intestinal tract always coexists. There seems to be a dearth of statistical information regarding this subject. In a survey of the literature there appears to be numerous statements regarding the association of gall bladder disease and irritable conditions of the gastro-intestinal tract, but as far as I can ascertain from the available literature, no large series of cases have been seen studied previously to show the comparative difference between the number of colopathies

found in the normal and those found in the pathological gall bladder groups. Since some attention has been focused upon this subject, and since increasing importance has been attached to the effect of irritable states of the colon in its relation to gall bladder disease, the necessity for a detailed statistical study offers a factual basis for an opinion regarding the association of these conditions. This communication is therefore concerned with a statistical study in order to correlate the coexistence of the various colopathies in cases of normal and pathological gall bladders observed in the routine roentgenologic examinations.

A survey was made of 230 consecutive cases, on whom a gall bladder visualization test and a gastro-intestinal or colon enema examination had been made,

in order to determine whether colopathies are more commonly observed in diseased gall bladders than in normal ones. Of the 230 gall bladder cases, 130 were normal and 100 pathological. A comparative statistical study of the results obtained is shown in Table I.

TABLE I

	Normal Gall Bladders Per Cent	Pathological Gall Bladders Per Cent
Irritable or unstable colon	76	61
Colonic stasis	20	29
Diverticulosis	3	7
Redundant colon	1.5	6
Ulcerative colitis	0	1
Carcinoma	1.5	0

Table I yields conclusive evidence that colopathies are not encountered more often coexisting with gall bladder disease than with normal gall bladders.

The cases with irritable or unstable colons were further subdivided roentgenologically into the spastic, hyperirritable and mucous colitis varieties as shown in Table II.

TABLE II

	Normal Gall Bladders Per Cent	Pathological Gall Bladders Per Cent
Spastic colon	27	12
Hyperirritable colon	31.5	31
Mucous colitis, with demonstrable string sign	17.5	21

Table II reveals a greater number of cases of spastic colons in the normal gall bladder series than in the pathological group. However, in the other varieties of irritable colons, there was no significant difference. These studies indicate that irritable colonic conditions do not invariably accompany gall bladder disease.

It is noteworthy to point out that Moore found that irritable colons are commonly observed in gall bladder disease, while Kunath states that the association of an irritable gastro-intestinal tract is a frequent occurrence in cases of flatulent dyspepsias of so-called cholecystitis, and suggested the possibility of the co-existence of an associated spastic biliary tract. Lahey and Jordan on the other hand assert that a non-filling gall bladder is at times attended by colonic irritability. They reported a series of 65 cases of colonic irritability of which 44 per cent revealed a non-filling or inadequate filling gall bladder, which became normal after 5 to 10 days of bowel management. However, their observations have not been in accord with others,

but notwithstanding their views, our experience indicates that the various colopathies do not interfere significantly with the filling of the normal gall bladder.

Intestinal stasis is also believed to be more prevalent in gall bladder disease. In this study, colonic stasis occurred in 20 per cent of the normal and in 29 per cent of the pathological gall bladders. This apparent increase of cases of colonic stasis in the pathological group is no doubt due to the larger number of cases with redundant colon, which is commonly associated with colonic stasis. It may be concluded from this study that colonic stasis is not materially increased in gall bladder disease.

Sluggish emptying of the stomach and the small intestine is not infrequently seen in gall bladder disease. However, in most instances the stomach is completely empty in the six hour examination. The small intestine is also empty between the 10 to 12 hour period. No abnormal dilatation of the small intestine was observed in our cases, except for a few instances of slight dilatation of the lower ileum. The effect of motility of the small intestine has been studied by Bayer, who observed a sluggish motility and dilatation of intestinal loops in the small intestine in hepatobiliary disease. He points out that bile has an inhibiting influence on the smooth muscles and that if bile enters the blood stream, the tonus and peristalsis are reduced.

SUMMARY

Conclusive evidence is shown that colopathies are not necessarily an accompaniment of gall bladder disease. A comparative study of 230 cases of various colopathies associated with normal and pathological gall bladders clearly show that the occurrence of colopathies is not dependent upon the condition of the gall bladder. The role in which irritable colon plays in gall bladder visualization is undoubtedly a minor one. Colopathies do not profoundly affect the cholecystographic test, and in our experience non-filling or inadequate filling of the gall bladder cannot be attributed to these conditions.

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Biophotometric Studies in 30 Cases of Chronic Ulcerative Colitis*

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I. INTRODUCTION

THE problem of ulcerative colitis with reference to nutritional deficiency deserves greater interest. The search for an etiologic agent or a therapeutic

measure has overshadowed the other aspects of this disease.

The severity of the symptoms often causes the physician to focus his attention upon the alleviation of the most disturbing factor—the diarrhea. The maintenance of body nutrition in these markedly asthenic,

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emaciated individuals who have no desire to eat is a problem that has taxed the ingenuity of many clinicians. Most men have felt that such patients should have frequent feedings of highly nourishing, low-residue foods with large amounts of additional vitamins. The only basis for this idea was the occasional case with symptoms due to avitaminosis, seen in patients who were sick over long periods of time. There was no laboratory evidence that these individuals had diminished vitamin resources or had failed to utilize the vitamins supplied them.

The development of the deficiency syndrome usually does not manifest itself with any obvious clinical evidence until well along in the course of the disease. It is not until the late stages that the symptoms of diarrhea may be overshadowed by the changes attributable to avitaminosis.

The signs and symptoms of avitaminosis are manifold, being determined by the particular deficiency (1). The clinically observable changes which can be attributed to Vitamin A deficiency are rarely seen in the early stages of ulcerative colitis. The full-blown picture of epithelial hyperplasia, metaplasia, keratinization with night blindness and xerophthalmia is known far better in the laboratory animal than in the human. Yudkin (2) and Yudkin and Lambert (3) in 1923 working with rats found that by feeding these laboratory animals a diet deficient in fat soluble Vitamin A they were able to reproduce ocular conditions similar to the disease known as xerophthalmia in humans. On one occasion we have seen this picture in a patient with long standing disease.

Specific lesions of the skin were early described by Kiel and Scheer (4). Cases combined with xerophthalmia and hemeralopia have been described by Frazier and Hu (5), Loewenthal (6) and Nicholls (7) reported several instances of night-blindness. Youmans and Corlette (8) were the only ones who studied cases of Vitamin A deficiency with a visual photometer and demonstrated that hemeralopia existed in many instances.

Our series, we believe to be the first report of a biophotometric study of Vitamin A deficiency in a fair series of cases of ulcerative colitis.

The question whether or not ulcerative colitis is fundamentally a manifestation of a deficiency has occurred in the literature at regular intervals.

Crohn (9) in 1924 reported the occurrence of peculiar ocular conditions, associated with ulcerative colitis in two women who had been on restricted dietary regimens for prolonged periods of time and where the ocular manifestations cleared completely within several days with a change from a restricted diet to one complete in all vitamin factors particularly Vitamin A. He suggested "that the ophthalmic picture was in some way a nutritional deficiency phenomenon analogous if not identical with xerophthalmia. T. T. Mackie (10) in reviewing the problem in 1935 made a pertinent observation in which he said "it is a difficult topic to discuss because the factor of opinion enters so largely into the interpretation of the clinical phenomena. It is not easy to adduce evidence which is clear cut and beyond criticism."

We and others have felt that an objective method for determining clinical states of avitaminosis A is highly desirable. Such a method we thought would be of advantage in determining if their gastro-intestinal

tract showed deficiency states attributable to or concomitant with these disturbances.

II. DISCUSSION OF METHOD

It was not until 1934 that a new method was made available for estimating any of the intermediate phases of Vitamin A deficiency. At that time Jeans and Zentmire (11), using a photometer, tested the sensitivity to light following partial dark adaptation in a group of children.

In 1937 a new apparatus, known as a Biophotometer, was described by Jeans et al (12). It was based on the theory that the rods in the retina contain a substance termed "visual purple." This substance is very sensitive and becomes bleached and inactive when exposed to light but is rapidly regenerated if a sufficient supply of Vitamin A is present in the body.

Fredericia and Holm (13) showed that Vitamin A was the precursor substance of visual purple. Wald (14) demonstrated that Vitamin A was present in large amounts in the retina. The work of K. Tansley (15) indicated that a subnormal intake of this vitamin in the body caused depleted body stores which in turn lead to slow and poor regeneration of the visual purple. Without an adequate supply of regenerated visual purple the retinal rod cells become less sensitive. This leads to the clinical condition known as "hemeralopia" or poor vision under dim illumination which can be detected in all degrees by use of the biophotometer.

Briefly, the biophotometer is used as follows: The observations are made by determining the amount of light necessary for the subject to see three of the five points of a dice five-spot (or quincunx) punched out of a metal screen, when the light transmitted through the holes is of decreasing intensity from the left to the right of the quincunx screen. Thus, the essential features of the instrument include a bright light, a quincunx screen, and a dim light of controllable variability of intensity for illumination through the holes of the quincunx. The total test time is twenty-three minutes divided into three periods: (1) a ten minute "fore-period" in the dark, (2) exposure to the bright light of the photometer for three minutes and (3) a ten minute period in the dark known as "after period." Readings are made at the beginning, middle and end of the "fore-period" and for the last ten minutes or "after period" every two and one-half minutes and consist of turning the rheostat handle on the dial until the subject sees only two spots and then turning it slowly back until a third spot is again just visible. This is known as an "end-point" and the dial reading is recorded. This reading is in turn converted into millifoot candles by means of a standard chart.

Since its introduction the biophotometer has been used in many clinics throughout the country (11, 12, 16, 17, 18). The value of this instrument for the determination of A-Avitaminosis within a certain range, has been accepted. However we realize that the question is not definitely solved.

Our attention was drawn to the possibility of using this method in a study of cases with ulcerative colitis. It was true that most of our cases were receiving large doses of vitamins, on an empirical basis, but we were interested in determining the adequacy of their medication. We were likewise concerned with the adequacy

of their diets during the "acute," "interval" and "healed" phases. We felt that by using the biophotometer we might obtain objective data which would not be open to the criticism offered to purely subjective observations.

In Mackie's (19) series of 75 cases, 62% showed evidence of avitaminosis, but none of the patients exhibited night blindness or xerophthalmia. Many of them showed skin changes attributable to vitamin deficiency, which he noted appeared in spite of dietaries which were completely adequate for the normal individual. As a result, he concluded that the deficiency of vitamins contributed to the maintenance of the disease, but could offer no definite evidence.

E. C. Davis (20) in approaching the problem refers to the relationship between the disease and avita-

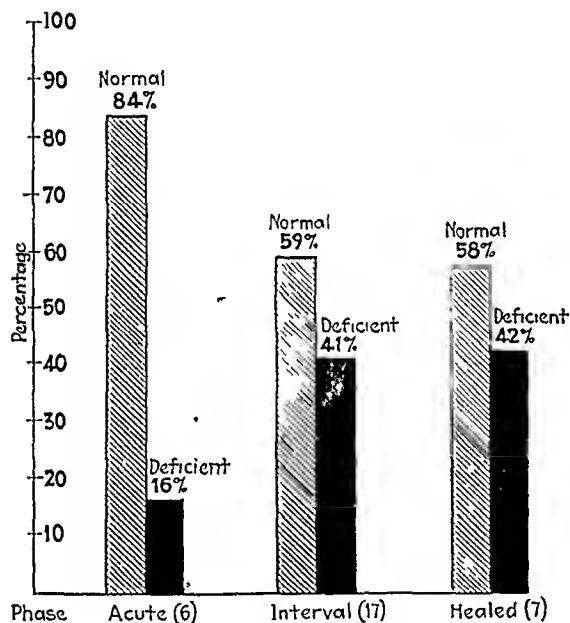
are the terms "acute," "interval" and "healed," which we define as:

Acute Phase: Fever, cramps, tenesmus, diarrhea with bloody, purulent, loose stools. Sigmoidoscopic findings show purulent, sanguinous discharge with many bleeding ulcerating points in an edematous beefy mucous membrane. X-ray shows changes interpreted as or diagnostic of ulcerative colitis.

Interval Phase: Recovered from an acute phase and now has no fever, cramps or tenesmus. Has occasional slight bloody staining of well-formed or semi-solid stool. Sigmoidoscopic finding shows a granular mucosa (frosted glass type)—few healing ulcers which may bleed on wiping. X-ray may or may not show evidence of old colitis.

Healed Phase: Long uneventful period with no clinical or sigmoidoscopic findings. X-ray evidence may be minimal or not present.

BIOPHOTOMETRIC STUDIES IN 30 CASES OF CHRONIC ULCERATIVE COLITIS



minosis but makes no definite statement and mentions Vitamin A but briefly. Therapeutically some authors have approached the problem from another viewpoint. The French literature (21, 22) has several publications on the treatment of recto-colitis with large doses of carotene mixed in olive oil and given as retention enemas. Although the reports are favorable, no interpretation is advanced as to the method of action of the treatment. Spiegel (23) at The Mount Sinai Hospital has had a limited experience with the use of retention enemas of cod liver oil and speaks favorably of the method. Best (24) also speaks well of the use of cod liver oil in cases of ulcerative colitis.

III. DEFINITIONS

We have attempted for the sake of clarity and brevity to classify our cases according to the phase of the disease in which the patient was found at the time of the test. The word "phase" is used advisedly as

IV. RESULTS

As far as we know, no attempt had been made to estimate the Vitamin A reserve capacity of these patients. We felt it would be interesting to do so and present our report on thirty proven cases of chronic ulcerative colitis. All of these cases have been known to have colitis for some period of time, having been treated, either on the wards or out-patient department at The Mount Sinai Hospital. Two of the cases had ileostomies which resulted in marked clinical improvement, although they still had the diseased colon.

Of the cases studied, eleven (30%), showed evidence of inability to adapt normally in the dark. This percentage is higher than that in the general population, in or outside of a hospital, and is indicative of a Vitamin A deficiency existing among the general group of patients with ulcerative colitis. If we eliminate from our calculations those cases known to be receiving massive doses of vitamins (hospitalized cases), the value for the group rises to 41%.

The concomitant existence of poor dark adaptation with disease of the gastro-intestinal tract in such a percentage of cases is made more significant when we analyze the entire group. We were fortunate in having the opportunity to study a varied group in which all phases of the disease were observed.

Six "acute" cases were studied while in the hospital. Of this group only one (16%) case showed a deficiency of dark adaptation. All of the remaining patients (84%) showed fairly normal curves. On examining the case histories, the explanation for this finding was found in the fact that all the hospitalized cases with the exception of the one with poor adaptation were receiving massive doses of Vitamin A in form of Cod Liver Oil. In this particular instance where a Vitamin A deficiency existed, the patient was refusing all nourishment. She had been acutely ill for a long period of time and had been vomiting in addition to having severe, almost intractable diarrhea. Her dark adaptation curve was the lowest seen in the entire study. Shortly after the test, she developed marked changes of the skin and a severe conjunctivitis.

Of the remaining five cases, three were children who were routinely receiving large doses of Vitamin A in form of Cod Liver Oil as were the other two adults. It was obvious from this small group that absorption of Vitamin A would take place in the patient acutely ill with colitis if sufficiently massive doses of

vitamins were given. However, the ability to absorb vitamins as compared with normals is probably diminished as evidenced by the next group.

Seventeen of the cases from the out-patient department were studied in the "interval" phase of their disease. Of this number, seven (41%) showed evidence of Vitamin A deficiency as determined biophotometrically. Since the figure for studies of general hospital population shows an average deficiency of dark adaptation in 20% of cases studied, our figure of 41% for the group of patients who presumably are recovering from colitis is definitely informative. We have not lost sight of the fact that these patients come from a group (out-patient department) that occupies a lower economic level which influences their dietary regime. Nevertheless, the difference between 20% as found by others in similar groups and 41% in our group permits the conclusion that a greater percentage of patients with "interval" ulcerative colitis show evidence of Vitamin deficiency than would be normally expected. It indicates that the disease may play a part in the development of this deficiency in many instances. This observation is made more obvious by study of the following group.

In this particular group of "healed" cases, only seven instances were studied. Most of these patients were being seen very infrequently at the out-patient clinic because they felt well. Of this group three were proven to have poor dark adaptation. Here again we were surprised to find that in this group of apparently healthy cases there was a higher incidence showing Vitamin A deficiency than we would normally expect. Basing our expectancy on other studies, we should expect only one or none of these patients to show evidence of a deficiency. That their deficiency was conditioned to some extent or dependent upon their previous disease, seems more than likely.

The hypermotility of the gastro-intestinal tract which has been advanced in explanation of the cause of the deficiency syndrome, in the acute cases, is merely another factor, as evidenced by the subclinical avitaminosis already found to be existing in the interval and healed phases. It is more likely that there is a disturbance of the ability to absorb the vitamins from the intestine. The disease is probably not limited

to the colon, but includes functional and anatomic alterations of the small bowel. A rapid passage of food to the colon, does not, to our knowledge, occur in the interval or healed phase.

Even though our group of cases is small, we feel the data is significant. We were surprised to find such a large percentage of Avitaminosis A in a group whose dietary instructions included emphasis on the intake of vitamins. On the basis of the existence of a greater percentage of poor dark adaptation in our group, as compared to general hospital groups, we think that the Avitaminosis A is due to the disease common to our patients.

Our conclusions are naturally based on the acceptance of the reliability of the biophotometer for the determination of Vitamin A deficiency.

We feel, that judging from the apparent deficiency of Vitamin A in this report, we may speculate the probability of the existence of multiple Vitamin deficiencies and that an attempt should be made to correct these by the administration of large amounts of all vitamins even during the "healed" phase.

SUMMARY

The objective evidence of Avitaminosis A, as obtained by means of the biophotometer, indicates that in our group of 30 cases of chronic ulcerative colitis:

(1) 41% have a subclinical Vitamin A deficiency—(twice the "normal" expectancy).

(2) The phase of the disease, "acute," "interval," "healed," does not influence the occurrence of the Vitamin A deficiency in our series.

(3) Acutely ill patients receiving massive doses of Vitamin A show normal dark adaptation. Chronically ill patients show deficient dark adaptation. Healed patients show deficient dark adaptation.

(4) There appears to be more than a casual relationship between Avitaminosis A and ulcerative colitis.

(5) The ability to absorb Vitamin A given in normal amounts is diminished in ulcerative colitis.

(6) The disease predisposes to Avitaminosis A.

(7) The high percentage of Avitaminosis A in the interval and healed phases indicates the need of larger doses of vitamins prophylactically.

With the technical assistance of Mrs. Clara Lewis.

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The Effect of Certain Parenterally Administered Drugs on the Colon of the Dog*

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REPORTS on the effects of certain of the newer drugs and biologic preparations on the motility of the gastro-intestinal tract reveal much conflicting evidence. This is not surprising because different species of animals were used and a wide variety of methods were followed by the various workers. Furthermore, some investigators obtained their results from animals under general anesthesia, whereas others studied the response of the gastro-intestinal tract of unanesthetized animals and still others studied a perfused isolated segment of intestine. The present report is concerned with the action of certain drugs and biologic preparations on the colon of the intact dog. This study was undertaken in the hope that some of the conflicting data might be reconciled and that additional information on the action of certain drugs and biologic preparations might be obtained. The drugs investigated were epinephrine, ephedrine, histamine, pituitrin, pitocin, pitressin, acetylcholine, physostigmine, hypertonic solutions of sodium chloride, hypertonic solutions of glucose, calcium salts and parathyroid extract.

METHODS

A group of six preoperatively trained dogs were prepared under ether anesthesia with either Thiry or Vella fistulas for experimental purposes. The preparations of the respective fistulas have been described by Bargen, Osterberg and Mann and by Larson and Bargen. The isolated loop of gut consisted of practically the entire colon, the only part of the colon not included consisting of a portion 5 to 6 cm. in length immediately proximal to the anus. It was possible to use the dogs repeatedly without administering anesthetic agents which might conceivably influence the action of the drugs administered.

Two methods of recording were used in determining the effect of the drugs on intestinal motility. For the dogs with Thiry fistulas a constant pressure method was devised.‡ This constant pressure method proved of particular value in recording the effect of drugs producing depression of tone and motility in the colon, because an approximately quantitative effect could be

obtained and recorded. The balloon method of recording was used in experiments performed on dogs with Vella fistulas, utilizing water manometers for recording purposes. Tracings of motility were taken from both the transverse and sigmoid portions of the colon simultaneously with this method.

A total of 160 experiments was performed. Each drug was used in at least six experiments and, with the exception of parathyroid extract, both methods of recording were used with each drug.

RESULTS

Epinephrine (adrenalin). The depressant effect of epinephrine on gastro-intestinal tone and motility was shown by Langley, Dixon (13), Elliott and many other investigators but according to the work of Hoskins (25), Gruber, Daniélopou and his co-workers and others a dilute solution of epinephrine may stimulate the intestine.

In seven experiments epinephrine was injected intravenously into six dogs. Doses of 0.1 to 0.2 cc. of a 1:1000 solution produced very brief and temporary relaxation and inhibition of motility of the colon (Fig. 1, upper left). The period of quiescence lasted from thirty to one hundred twenty seconds, after which normal motility returned. The subcutaneous administration of epinephrine in doses as high as 0.5 cc. of a 1:1000 solution evoked no response whatsoever in five experiments.

Ephedrine. Ephedrine, like epinephrine, produces inhibition of intestinal tone and motility; moreover, this action is much more prolonged than that of epinephrine. Amatsu and Kubota first noted this property, but it remained for Chen and Schmidt to investigate this phenomenon pharmacologically; they noted the effects of the drug after nicotine and pilocarpine had been administered. Trachtenberg by means of roentgenologic observations found that ephedrine caused a marked decrease in the emptying time of the stomach as well as decreased motility of the stomach and intestines of human beings. Several workers, in particular Kinnaman and Plant, found that large doses of ephedrine have a stimulative action on gastro-intestinal motility in the dog. These workers observed that after section and degeneration of the extrinsic nerves of the bowel, ephedrine caused stimulation of activity of the bowel. This result they attributed to stimulation of Auerbach's plexus by ephedrine.

Ephedrine was injected intravenously into six dogs with Thiry or Vella fistulas in a series of seven experiments. This drug produced moderate relaxation of tone and decreased motility. Doses of 1 to 5 mg. per kilogram of body weight were injected subcutaneously and intravenously, the larger doses giving more striking and lasting inhibition than the smaller ones. The inhibition from 5 mg. per kilogram of body

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‡The apparatus for the constant pressure method consists essentially of a horizontal, graduated, glass tube 2 meters in length having a bore of 6 mm. This horizontal tube is maintained at a level of 10 cm. above the stomach of the Thiry fistula. A catheter with multiple fenestrations distally is attached to one end of the tube; the other end of the tube is left open. The catheter is then inserted into the Thiry loop and the whole system is filled with a nonabsorbable, physiologically isotonic solution (either a 4.7 per cent solution of sucrose or a 1.25 per cent solution of magnesium sulfate). Hence, with changes in motility of the bowel, the column of fluid in the open, horizontal tube fluctuates back and forth. Readings from the fluctuation of the meniscus which forms toward the open end of the tube are taken at intervals of twelve seconds and the results are plotted.

Submitted February 5, 1939.

weight intravenously lasted usually from one to three hours (Fig. 1, upper right).

Synergistic effect of ephedrine and physostigmine.
In five experiments using from 0.25 to 0.4 mg. of

physostigmine subcutaneously an appreciable effect was not noted. However, in five experiments using physostigmine in similar doses after the intravenous injection of 20 to 30 mg. of ephedrine, a marked and

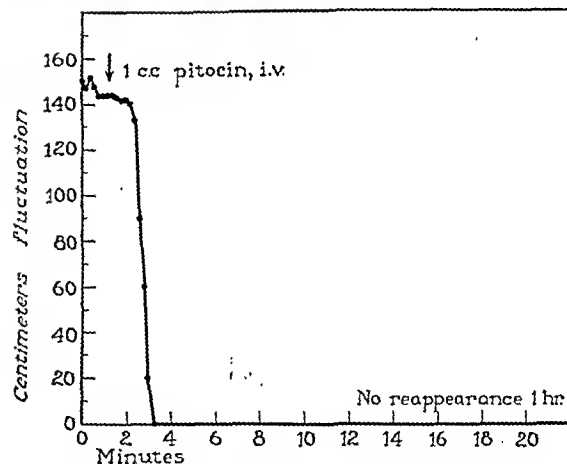
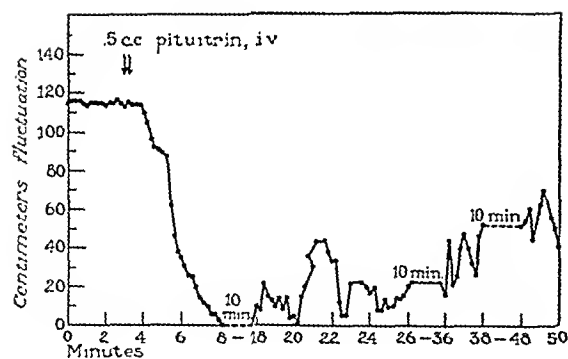
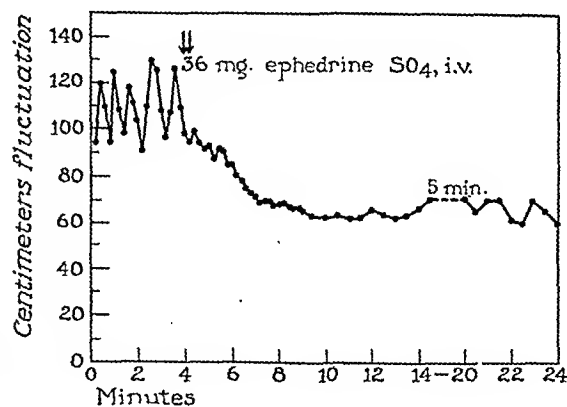
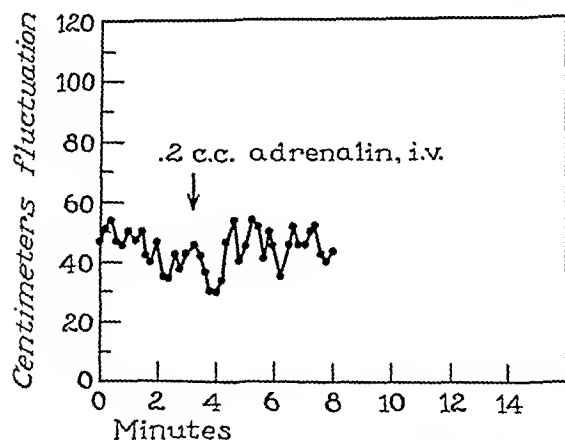


Fig. 1, upper left (dog No. 1). Effect of intravenous injection of epinephrine (adrenalin) as recorded by the constant pressure method in a Thiry loop; upper right (dog No. 2). Effect of intravenous injection of ephedrine sulfate as recorded by the constant pressure method in a Thiry loop; middle (dog No. 6). Synergistic effect of physostigmine and ephedrine. The colon had been relaxed by the intravenous injection of 20 mg. of ephedrine fifteen minutes prior to the subcutaneous injection of the physostigmine. Record made by the balloon method in a Vella loop. Upper tracing from the transverse colon. Lower tracing from the sigmoid; lower left (dog No. 1). Effect of intravenous injection of pituitrin as recorded by the constant pressure method. Note that the depression of tone and of motility is not nearly so great as that produced by pitocin (Fig. 1, lower right) and the depressive effect is not so prolonged; lower right (dog No. 1). Effect of pitocin injected intravenously as recorded by the constant pressure method. Note the tremendous depression of tone which was incapable of being recorded. Both lower tracings were recorded by the constant method in a Thiry loop.

sustained increase in tone and motility of the gut was obtained (Fig. 1, middle).

Histamine. A number of workers including Guggenheim and Löffler, MacKay, Tidmarsh and others presented evidence to indicate that histamine produces an increase in the tone and motility of the intestines of experimental animals under anesthesia or with Thiry or Vella fistulas. On the other hand, Ivy and Vloedman reported that they could not observe any effect on the stomach, jejunum and ileum of unanesthetized dogs with fistulas after the injection of histamine.

Histamine was injected intravenously into six dogs with Thiry or Vella fistulas in a series of eight experiments. Doses ranged from 0.25 to 0.5 mg. In six of the eight experiments there was produced a mild depression of tone lasting from fifteen to twenty minutes with considerable irregularity in the motility of the colon. In the other two experiments, a moderate increase in tone lasting for a short interval occurred.

Pituitary preparations. There are many conflicting reports concerning the action of pituitary extracts on the intestine. Practically all of the early reports attributed to pituitary extracts the property of stimulating intestinal motility and peristalsis. Experimental and clinical evidence seemed to bear out this finding and it was assumed that pituitary extract had the ability to stimulate the smooth muscle of the intestine as well as that of the uterus. However, in 1916, Shamoff reported that pituitary extracts (both fresh and commercial) usually produced relaxation of the isolated intestine of the rabbit. Hoskins (26) in the same year reported that the intravenous injection of pituitrin caused depression of intestinal tone and of peristalsis in five of six dogs. Dixon (14) and Mordwinkin both reported that pituitrin seemed to have a markedly relaxing effect on the colon of experimental animals.

In 1928 Kamm and co-workers prepared the concentrated pressor and oxytocic fractions of pituitrin and soon a number of workers investigated the action of these fractions on the gastro-intestinal tract. Gaddum early noted that vasopressin (pitressin) had a much more powerful action in stimulating the intestines of rabbits than did oxytocin (pitocin). McIntosh and Owings noted that pituitrin, vasopressin and oxytocin, all had a depressive effect on the obstructed intestine of the dog. Gruber and Robinson made similar observations on the ileum of unanesthetized dogs, but noted that occasional spasm or "incomplete tetany" occurred, particularly after pitressin was administered. Carlson found that among dogs there usually occurred a depression of tone and motility, among rabbits there was a definite increase in motility, and among human beings there invariably occurred an increase in motility of the colon following the injection of pituitrin. Quigley and Barnes, and Ochsner, Gage and Cutting (46) also observed a depressive effect on the intestine of the dog. Melville and Stehle extracted the various pituitary fractions by their own methods and found the effects on the intestine of the dog identical with the effects of commercial pitressin and pitocin. Hence, they concluded that a third substance was not present. Guthrie and Barger concluded from their work on human beings with ileostomies and colostomies that pituitrin was the only effective drug for overcoming paralytic ileus.

Pituitrin. This drug was used in a series of twelve experiments in six dogs with Thiry or with Vella

fistulas. The extract was injected subcutaneously or intravenously in dosages of 0.1 cc. to 0.5 cc. In eight of the twelve experiments pituitrin produced a marked degree of inhibition only (Fig. 1, lower left). In two experiments significant changes were not noted and in the other two experiments moderate inhibition occurred and was followed by transitory stimulation. Inactivated pituitrin did not affect the motility of the colon of the dog. The method of inactivation was that described by Gaddum.

Pitocin. Remarkably striking results were obtained from the injection of this drug. Pitocin was used in ten experiments on six dogs. Intravenous and subcutaneous injections of the drug in doses of 0.5 cc. to 1 cc. produced in all experiments profound relaxation and complete inhibition of motility. This depressive effect lasted two to three hours or longer (Fig. 1, lower right). Control experiments in which inactivated pitocin was injected did not disclose any such inhibitory effect.

Pitressin. Varying results were produced by pitressin. When injected intravenously or subcutaneously in doses of 0.15 cc. to 0.3 cc. in twelve experiments on six dogs, the following results were recorded: 1. In two experiments transient augmentation followed by prolonged inhibition was obtained (Fig. 2, upper left). 2. In two experiments there was an initial, transient inhibition followed by increase in tone and motility lasting from four to six minutes which in turn was followed by inhibition lasting from thirty-three to fifty minutes. 3. In six experiments inhibition only was recorded, lasting ten minutes to one hour. 4. In two experiments the rate of contraction was accelerated, accompanied by a slight decrease in tone. Inactivated pitressin had no effect on motility.

Acetylcholine. In 1905, Magnus demonstrated that an extract could be obtained from the wall of the gut which had a stimulating action on intestinal motility. Weiland and le Heux investigated the substance pharmacologically and the latter worker identified the substance chemically as choline. Le Heux further demonstrated the markedly increased physiologic activity resulting from the acetylation of choline and advanced the hypothesis that choline was the hormone of gastro-intestinal motility. Dale investigated the action of various esters of choline and demonstrated that the potent ester, acetylcholine, was destroyed rapidly in the blood stream. He found that all the choline esters of choline were powerful stimulators of gastro-intestinal motility. Several observers, including Klee and Grossmann, Abel and others reported that acetylcholine was efficacious in the treatment of adynamic ileus.

In contrast to the reports just mentioned a number of workers including Mulinos (44), Carlson, Smith and Gibbins, Kratinoff and Novikowa, and Ochsner and co-workers (46) produced evidence indicating that acetylcholine or choline have either no effect or may even have a depressant action.

Frank, Zimmerman and Necheles made the interesting observation that acetylcholine given in conjunction with eserine produced a stimulating effect on the motility of the intestine in much smaller doses than was necessary if the drugs were used separately. Frank and his co-workers explained this effect as being due to the combined action of the two drugs rather than to the preservation of acetylcholine by physostigmine

as had been suggested by the work of Matthes and of Englehart and Loewi.

Solutions of acetylcholine hydrobromide were injected intravenously in doses of 0.5 to 1 mg. per kilogram of body weight. In six experiments acetylcholine produced moderate spasm of the colon (Fig. 2, upper right), the effect lasting from ten to twenty minutes. In two experiments a moderate increase in tone was produced. In four experiments, in which the drug was injected subcutaneously, little or no effect was noted as regards intestinal motility.

The experiments of Frank, Zimmerman and Necheles were repeated. When acetylcholine in doses of 0.2 mg.

to 0.3 mg. was given intravenously after the administration of 0.3 mg. to 0.4 mg. of physostigmine, rather marked activity of the colon resulted which lasted for thirty minutes or longer. When either of these two drugs were given alone in the respective doses just mentioned, an effect failed to be produced.

Hypertonic solutions of sodium chloride. Hughson and Scarff in 1924 were the first to report that the intravenous injection of hypertonic solutions of sodium chloride invariably produced an increase in intestinal tone and motility. Soon thereafter a large number of investigators, including Ross, Orr, Ochsner and co-workers (47) and many others published re-

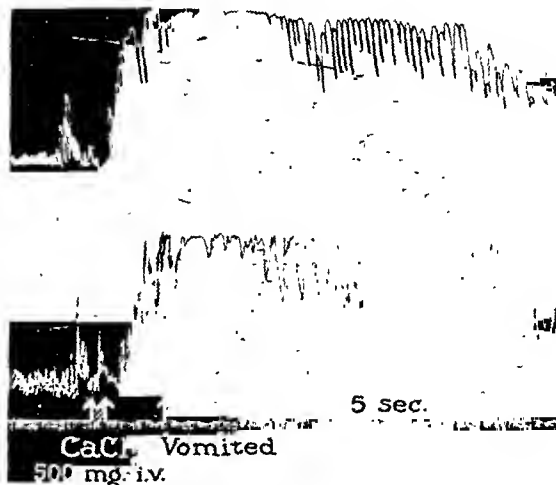
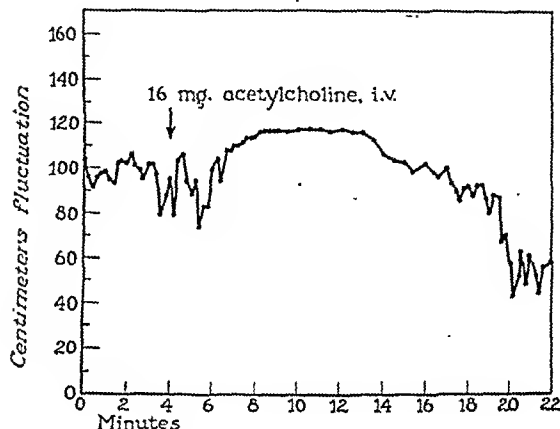
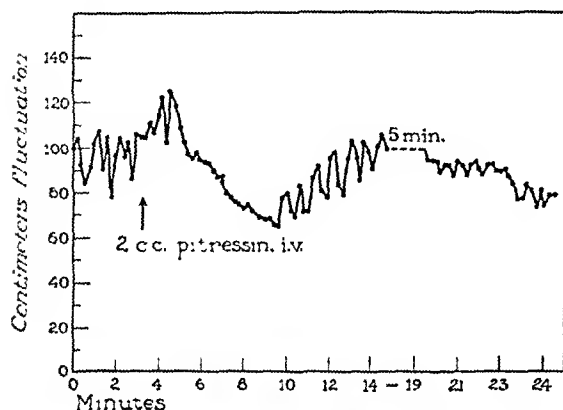


Fig. 2, upper left (dog No. 1). Effect of pitressin injected intravenously as recorded by the constant pressure method. Note that the depression of tone is not nearly so marked or so prolonged as that which followed the injection of pitocin or pituitrin; upper right (dog No. 3). Effect of intravenous injection of acetylcholine recorded by the constant pressure method. Note that a comparatively severe degree of spasm was produced; lower left (dog No. 5). Effect of hypertonic solution of sodium chloride intravenously as recorded by the balloon method. Note that a severe degree of hyperpnea was produced and that during relaxation of the gut the respirations were transmitted to and were recorded by the balloons. Upper tracing record of respiration; middle tracing from the transverse colon; lower tracing from the sigmoid; lower right (dog No. 5). Effect of calcium chloride injected intravenously as recorded by the balloon method. Upper tracing from the transverse colon; lower tracing from the sigmoid.

sults indicating that this stimulating influence occurred in every instance.

Hypertonic solutions of sodium chloride were used intravenously in a series of twelve experiments. In all twelve experiments an immediate increase in colonic tone, with some increase in motility was produced (Fig. 2, lower right). This effect lasted for twenty minutes in some instances. Control experiments using physiologically normal saline did not affect colonic motility, regardless of the rate of injection or the amount injected. However, very small amounts of a hypertonic solution of sodium chloride (as little as 2 cc. of a 20 per cent solution) produced a rather marked increase in tone. A 20 per cent solution seemed to be the optimal concentration to use, it being much more effective than a 10 per cent solution and just as effective as a 30 per cent solution.

Hypertonic solutions of glucose. Glucose has been considered to have a slight inhibitory action on intestinal motility. However, Quigley and Hallaran, Mulinos (45) and others could not find experimental evidence to bear out this belief.

Ten experiments were performed on six dogs using solutions of glucose in concentrations of 10 per cent, 20 per cent and 50 per cent. Ten cc. was injected intravenously within two minutes in each experiment. In eight of the ten experiments there was absolutely no evident change in tone or in motility; in the other two experiments there was an insignificant and transient increase in colonic tone.

Physostigmine. Cannon and Murphy, in 1907, produced ileus experimentally in cats and studied the effect of physostigmine by means of roentgenographic observations after a barium meal. They observed a marked increase in peristalsis following the injection of the drug. Martin and Weiss, Ochsner, Gage, and Cutting (45) and others reported that physostigmine seemed to be beneficial in stimulating intestinal motility.

On the other hand, Martzloff in a carefully controlled group of experiments, did not observe any beneficial effect resulting from the postoperative use of physostigmine and strychnine; in fact, the drugs seemed to have a deleterious effect.

Guthrie and Bagen in their work on human beings found the effect of physostigmine inconstant and uncertain, although the doses used were rather small.

Physostigmine was used in twelve experiments on six dogs. The experiments indicate that physostigmine produces rather marked spasm of the colon. The drug was injected intravenously in doses of 0.5 to 1 mg. Larger doses were necessary to obtain comparable effects when the drug was injected subcutaneously. In no experiment was there an increase in motility of the colon, the intestine apparently being unable to relax when an effective dose of the drug was administered.

Calcium salts. A number of investigators, including Alvarez, Salant and Washein and Benigni showed that calcium salts were capable of producing an increase in the tone and motility of isolated loops of intestine.

Cantarow was of the opinion that both motility and secretory activity were inhibited by calcium. Fitzhugh, Miller, Taylor and Aub could not detect any effect on peristalsis or on tone of dogs in which the ileum was obstructed after the injection of relatively large doses of calcium chloride.

A total of twenty experiments was performed on six dogs using both calcium chloride and calcium gluco-

nate intravenously. The doses used were as follows: calcium chloride, 50 mg. per kilogram of body weight; calcium gluconate 0.5 to 1 gm. for each animal. In every experiment a rather marked increase in tone and in motility of the colon was obtained (Fig. 2, lower right). The effect lasted ten to twenty minutes. Serum calcium values, taken at the height of stimulation, revealed that the concentration of calcium in the serum had risen not higher than 15.2 mg. per 100 cc., the rise generally being in the neighborhood of 14.5 mg. per 100 cc.

Parathyroid extract. Because calcium salts injected intravenously produced increased tone and peristalsis in the colon, it was decided to determine what effect the raising of the concentration of calcium in the blood by parathyroid extract would have on colonic motility.

Rose, Stucky and Cowgill found that gastric motility in dogs was not affected by parathyroid extract. The experiments of Mahler and Beutel on human beings were inconclusive although, in some instances, deepening of peristaltic waves in the intestines and stomach was observed after the injection of parathyroid extract.

Sheldon, Kern, and Hakansson studied the effect of parathyroid extract on the colon in three cases of Hirschsprung's disease and concluded that the extract resulted in considerable diminution in the size of the dilated colon, as well as in a more frequent and more complete evacuation of colonic contents.

The intravenous administration of large quantities of parathyroid extract failed to produce the desired rise in concentration of serum calcium. The subcutaneous injection of parathyroid extract produced the maximal rise in concentration of serum calcium in about eighteen hours. Tracings were taken by the balloon method every hour for twenty-four hours and samples of blood were taken every two hours during the experiments for a determination of the content of calcium. In three of six experiments performed on three dogs with Vella fistulas, a slightly increased depth of waves of contraction and a slight increase in tone occurred coincidentally with the rise in the concentration of calcium in the blood. In the other three experiments appreciable changes were not obtained.

COMMENT

The synergistic action of ephedrine and physostigmine is of considerable interest in that the depressant drug, ephedrine, is capable of powerfully enhancing the stimulative action of physostigmine. The mechanism of this phenomenon might be explained (as has been suggested by Kinnaman and Plant) by the stimulative action of ephedrine on Auerbach's plexus in addition to parasympathetic stimulation by the physostigmine.

In regard to the conflicting evidence on the action of pituitary products, it seems likely that different species react differently to these preparations. For example, of seventeen authors who reported on the action of pituitrin among human beings, sixteen reported that pituitrin causes an increase in motility of the intestine, whereas only one author was of an opposite opinion. In contrast to the above, twenty-two of twenty-four authors reported that pituitrin produces inhibition in the dog when the experiments are conducted with the intestines in situ. The majority

of workers indicated that pituitrin causes inhibition of activity among cats and increased activity among rabbits. Hence, it seems likely that there is a variable response to pituitary products among different species of animals, and that this probably accounts for many of the conflicting results recorded. An analysis of the literature reveals that isolated loop preparations also give very variable results and this may account for some of the discrepancies. Steggerda, Gianturco and Essex showed that pituitrin produces stimulation of the colon of the cat only after very large doses are administered. Hence, from an analysis of the literature, it seems likely that most of the confusion arises from three factors: (1) variations in reactions of different species of animals, (2) the inconsistency of reactions of isolated loops of intestine and (3) possible variations resulting from varying doses. Of these factors, the first seems to be the most important.

Possibly the most striking and unanticipated result obtained in these experiments was the profound depression of tone and motility of the colon after the injection of pitocin. Only by the use of the constant pressure method was this depressive action indicated, the balloon method being incapable of recording the true extent of relaxation because of inherent limitations. From these experiments it would seem that the oxytocic fraction is a strong depressor of tone of the colon among dogs. Pituitrin, containing both the oxytocic and pressor fractions, is a less potent de-

pressor; pitressin, from which most of the oxytocic fraction has been eliminated, seems to be only mildly depressant.

Calcium salts proved to have a rather marked stimulative action on the colon of the dog. The results obtained after the injection of parathyroid extract indicate that a state of hypercalcemia does not necessarily cause increased intestinal motility.

SUMMARY AND CONCLUSIONS

A series of experiments were performed on trained unanesthetized dogs having Thiry or Vella colonic fistulas in order to determine the effect of a number of drugs on the motility of the colon. The drugs were administered parenterally. Recordings were obtained by means of rubber balloons and also by means of a constant pressure apparatus. It was found that calcium salts, physostigmine, hypertonic solutions of sodium chloride and acetylcholine produced increased tone and increased motility. Pitocin, pituitrin, pitressin, ephedrine, histamine and epinephrine caused decreased tone and decreased motility. Pitocin produced the most striking depressive effect. Hypertonic solutions of glucose and parathyroid extract had little or no effect on colonic motility. Physostigmine, used in combination with ephedrine, produced very marked stimulation of colonic motility, as did the use of physostigmine and acetylcholine simultaneously.

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The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons With Disease of the Upper Part of the Abdomen

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ORDINARILY when duodenal contents are removed with a tube from the duodenum and the enzymatic activity is studied the stimulants of external pancreatic secretion are: (1) the mechanical irritation caused by the entrance of the tube into the duodenum, and (2) physiologic stimulation by the acid gastric secretion entering the duodenum. The strength of such stimulants is uncontrollable and variable, and the concentration of enzymes in the duodenal fluid obtained under these circumstances consequently will vary greatly from time to time. While the importance of data obtained in this manner has frequently been minimized, and with much reason, we frequently have felt that we obtained information which was of value in the differential diagnosis of various diseases. We therefore have not been willing to condemn the method entirely. Analyses of our data presented in the following pages show that while there are definite limitations to the information obtained in this manner, the method is of sufficient value to warrant its continued use until there is available a stimulant which will produce a maximal quantity of external pancreatic secretion at all times.

MATERIAL AND METHODS

The concentration of pancreatic enzymes was determined in samples of duodenal fluid taken from 111 persons, seventeen of whom were normal. Duodenal drainage was performed once on eighty-nine, or 80.2 per cent, twice on thirteen, or 11.7 per cent, three times on seven, or 6.3 per cent, four times on one, or

0.9 per cent, and six times on one, or 0.9 per cent of the 111 persons. Only one sample of duodenal contents was obtained from sixty-three, or 56.8 per cent of the 111 persons, two samples were obtained from thirty-two, or 28.8 per cent, three samples were obtained from ten, or 9 per cent, four samples were obtained from three, or 2.7 per cent, five samples were obtained from two, 1.8 per cent, and nine samples were obtained from one or 0.9 per cent. In short, in more than 85 per cent of the instances only one or two samples were obtained.

It has been the usual custom in studies of the concentration of pancreatic enzymes in the duodenal contents to choose samples unmixed with gastric contents and we followed this practice. When we were unable to secure such specimens, however, one as free of gastric contents as possible was taken. We soon found that most samples of bile contained enzymes but that this was not always true. We also found that samples of duodenal fluid which were free of bile often contained pancreatic enzymes in normal concentration.

The concentration of amylase and trypsin was determined by the method of McClure, Wetmore and Reynolds. The concentration of amylase is expressed in terms of grams of d-glucose liberated for each 100 cc. of duodenal contents. The concentration of trypsin is expressed in terms of grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents. The concentration of lipase was determined by the method of Crandall and Cherry and is expressed in terms of the number of cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents.

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THE VALUE OF THE CONCENTRATION OF ENZYMES IN ONE SAMPLE OF DUODENAL CONTENTS AS AN INDEX OF THE FUNCTIONAL CAPACITY OF THE PANCREAS

Wide variations occurred in the concentrations of enzymes in different samples of duodenal contents obtained from the same person. Thus, in the duodenal contents of one person who did not have any abdominal disease the concentration of amylase varied from 6.1 to 11.5 gm. of d-glucose per 100 cc. In another case the concentration of amylase was 0 in the first sample and 6.5 gm. of d-glucose per 100 cc. of duodenal contents in the second sample. In the same case the concentration of trypsin varied from 1.4 to 5.0 gm. of nonprotein nitrogen per 100 cc. of duodenal contents, and the concentration of lipase varied from 15 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents. Many similar examples may be cited in cases of organic disease of the liver or biliary tract. Further proof of the variability of the concentration of enzymes in the different samples may be found in the fact that in ten instances the concentration of amylase was 0 in the first sample and well within normal limits in the second sample examined while in six instances it was well within the range of normal in the first sample and 0 in the second sample. Similar behavior was noted in the concentration of trypsin and lipase.

A single determination merely indicates the enzymatic activity of the particular sample and does not

give reliable information regarding the secretory activity of the pancreas nor does the concentration in two or four samples necessarily give reliable information. When the concentration in the first, or the first few, samples is high, the ability of the pancreas to secrete normal amounts of enzymes is obviously normal, but if the concentration is low or absent, no statement should be made regarding the degree of pancreatic function until the concentration of enzymes in many samples has been determined.

THE RELATIVE AMOUNTS OF THE THREE ENZYMES IN THE DUODENAL CONTENTS

In most instances comparable amounts of the three enzymes are present. In some instances it was obvious that this was not the case. In a sample taken from a normal person the concentration of amylase was high (14 gm. of d-glucose per 100 cc. of duodenal contents) and the concentration of lipase was low (3 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents) while in another instance the amylolytic activity was low (1.3 gm. of d-glucose per 100 cc.) and the activity of lipase was high (148 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents). Such lack of parallelism in the concentration of pancreatic enzymes in duodenal fluid deserves further investigation.

THE INCIDENCE OF DIFFERENT CONCENTRATIONS OF PANCREATIC ENZYMES IN THE DUODENAL FLUID

The incidence of different concentrations of the

TABLE I
Concentration of amylase* in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas

Physical Condition	Number	Grams of d-glucose liberated for each 100 cc. of duodenal contents												High Concentration*	Low Concentration*
		0	0.1-2	2.1-4	4.1-6	6.1-8	8.1-10	10.1-12	12.1-14	14.1-16	16.1-18	18.1-20	20.1-22		
Normal subjects	17	0	2	2	1	5	1	2	3	1				16	1.3
Intrahepatic jaundice resulting from cirrhosis of the liver or hepatitis	31	4	3	9	7	3	4	1						12.5	0
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	25	4	9	4	1	4	2						1	20.5	0
Obstructive jaundice resulting from carcinoma (15 cases)															
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	6	4	1		1									4.6	0
Complete biliary obstruction; carcinoma of the common bile duct	3	1		1	1									4.3	0
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	6	1	3	1	1									4.6	0
Biliary disease and subacute interstitial pancreatitis	10	2	1	2	2	2	1							8.5	0
Chronic pancreatitis with steatorrhea	7	7												0	0
Nontropical sprue	6	0	2	1	2				1					14	1.3

*Expressed as grams of d-glucose liberated for each 100 cc. of duodenal contents.

three enzymes observed in the duodenal contents of the 111 persons are given in Tables I, II and III. When the concentrations were determined in more than one sample obtained from one person, only the highest concentrations encountered have been included in the tables.

Normal persons. Among the seventeen normal persons, the concentration of amylase varied from 1.3 to 15 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 1.3 to 11.5 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 3 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III).

The variability of the concentration of enzymes is thus seen to be extremely wide in samples of duodenal fluid taken from normal persons under the conditions described. Our attention has previously been called to this wide variability in the range of concentration of pancreatic enzymes in the duodenal fluid obtained from normal persons, by the report of the Special Committee on Enzymes of the American Gastro-Enterological Association for 1935. When material is collected under the conditions described the complete absence of enzymes in the duodenal fluid alone points to a pathologic alteration in the capacity of the pancreas to secrete enzymes, but only when a complete absence of the enzymes is found at repeated examinations.

Patients with intrahepatic jaundice caused by cirrhosis or hepatitis. Since we had no reason for believing that the pathologic process involved the pancreas as well as the liver in the thirty-one cases in which intrahepatic jaundice was due to cirrhosis or hepatitis, we expected to find pancreatic enzymes present in the same amounts found in the duodenal contents of persons who did not have any disease of the pancreas or liver. This proved to be the case, for

the values varied through about the same range found in the duodenal contents of normal persons. Thus, the concentrations of amylase varied from 0 to 12.5 gm. of d-glucose per 100 cc. (Table I), the concentration of trypsin varied from 0 to 6.7 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 2 to 115 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of the duodenal contents (Table III). Amylase and trypsin were absent in single samples taken from five of the thirty-one patients in this group but other specimens showed that amylase or trypsin, or both were present in two of the five cases. If additional samples of duodenal contents had been examined, it is probable that the enzymes also would have been found in the remaining three cases. Again it is to be emphasized that many samples must be examined before deciding that pancreatic function is low or absent.

Patients with surgically verified obstructive jaundice caused by a stone in, or a stricture of, the common bile duct. In twenty-five cases in which obstructive jaundice was due to a stone in, or a stricture of, the common bile duct, and in which the surgeon found no evidence of pancreatitis, we found that the range of concentration of pancreatic enzymes was as wide as it was among normal persons. The concentration of amylase varied from 0 to 20.5 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 0 to 9 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 1 to 172 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III). In two cases amylase and trypsin were both absent. In both of these cases only one specimen was examined and it should not be concluded that obstructive jaundice which is the result of stone or stricture and which is not associated with

TABLE II

Concentration of trypsin* in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas

Physican Condition	Num- ber	Grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents										High Concen- tration*	Low Concen- tration*
		0	0.1-2	2.1-4	4.1-6	6.1-8	8.1-10	10.1-12	12.1-14	14.1-16			
Normal subjects	17	0	2	5	5	4	1	1			11.5	1.3	
Intrahepatic jaundice resulting from cir- rhosis of the liver or hepatitis	31	5	3	9	11	3					6.7	0	
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	25	3	3	11	7						9	0	
Obstructive jaundice resulting from carci- noma (15 cases)													
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	6	5	1								1.1	0	
Complete biliary obstruction; carcinoma of the common bile duct	3	1		1		1					8.3	1	
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	6	1	3	2							3.2	0	
Biliary disease and subacute interstitial pancreatitis	10	2	3	3	1	1					6.3	0	
Chronic pancreatitis with steatorrhea	7	6	1								1.5	0	
Nontropical sprue	6	0	1	1	1	2	1				9.4	1.7	

*Expressed as grams of nonprotein nitrogen liberated for each 100 cc. of duodenal contents.

pancreatic disease leads to loss of pancreatic function.

Surgically verified obstructive jaundice resulting from carcinoma of the head of the pancreas and the ampulla of Vater or common duct. Carcinoma of the head of the pancreas or carcinoma of the ampulla of Vater produced incomplete obstruction of the common bile duct (bile in the duodenum) in six instances and complete obstruction (no bile in the duodenum) in six cases. Amylase, trypsin and lipase (Tables I, II and III) were usually absent, or when they were present the concentration was low in the cases in which obstruction was complete; on the other hand, the enzymes were present in low moderate concentration in the cases in which obstruction was incomplete. In other words, when the obstruction of the common bile duct that is caused by carcinoma of the head of the pancreas or of the ampulla of Vater is complete, the obstruction of the pancreatic duct, as a rule, is also complete, and vice versa. However, the common bile duct may be completely obstructed and the pancreatic duct patent, as occurred in one case.

In the three cases of carcinoma of the common bile duct, the lesion produced complete obstruction of the common bile duct above the juncture of the pancreatic duct and common bile duct. In each case the enzymes were present in normal amounts, as one would expect.

When bile and pancreatic enzymes are both repeatedly absent from the duodenal contents, it may be assumed that both the common bile duct and pancreatic duct are obstructed. The carcinoma in such cases must be situated at the head of the pancreas or at the ampulla of Vater in order to obstruct both the common bile duct and the pancreatic duct. When bile is repeatedly absent and pancreatic enzymes are present in

the duodenal contents, the lesion may be situated in the head of the pancreas, at the papilla of Vater or in the common bile duct. The demonstration of enzymes in the duodenal contents will aid in the localization of the malignant lesion obstructing the common bile duct only when both bile and pancreatic enzymes are absent. The repeated absence of bile from the duodenum of a jaundiced patient is usually proof that the jaundice is obstructive. The malignant nature of the obstruction must be determined from the clinical history, by the palpation of a distended gall bladder and by the behavior of the concentration of bilirubin. The demonstration of the absence of pancreatic ferments in the duodenum may be important confirmatory evidence of the malignant nature of the obstruction and may be important in cases in which the abdomen is difficult to palpate.

Both bile and enzymes are usually present sooner or later in the duodenal contents of patients who have both intrahepatic jaundice and jaundice that is due to incomplete obstruction of the common bile duct by carcinoma; therefore, the demonstration of enzymes in the duodenal fluid will not aid in the differentiation of intrahepatic jaundice and jaundice caused by incomplete malignant obstruction. Crohn (2, 3, 4) has pointed out the value of the determination of the duodenal enzymes in the differential diagnosis of the types of jaundice and in the diagnosis of the situation of the obstruction.

Biliary disease associated with subacute interstitial (edematous) pancreatitis. In each of the ten cases in which biliary disease was associated with pancreatitis the surgeon described the pancreas as being enlarged,

TABLE III

Concentration of lipase in the duodenal contents of normal persons and patients with various diseases of the biliary tract and pancreas*

Physical Condition	Number	Cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents											High Concentration*	Low Concentration*
		0	1-20	21-40	41-60	61-80	81-100	101-120	120-140	141-160	161-180	181-200		
Normal subjects	9		2	0	2	1	1			1	1	1	179	3
Intrahepatic jaundice resulting from cirrhosis of the liver or hepatitis	11		4	3	1		1	2					115	2
Obstructive jaundice resulting from a stone in, or a stricture of, the common bile duct	14		3		3	2	3	1	1		1		172	1
Obstructive jaundice resulting from carcinoma														
Complete biliary obstruction; carcinoma of the head of the pancreas or ampulla of Vater	4	1	3										9	0
Complete biliary obstruction; carcinoma of the common bile duct	3		2								1		143	3
Incomplete biliary obstruction; carcinoma of the head of the pancreas or the ampulla of Vater	4		2		2								59	3.6
Biliary disease and subacute interstitial pancreatitis	4	2				1	1						109	0
Chronic pancreatitis with steatorrhea	5		5										19	1.5
Nontropical sprue	5		1	1		1	1				1		163	6

*Expressed as cubic centimeters of twentieth-normal solution of sodium hydroxide necessary to neutralize the fatty acids liberated by 1 cc. of duodenal contents.

edematous or indurated. The degree of abnormality was grade 2, on the basis of 4, in two cases, grade 3 in six cases and grade 4 in two cases. In these cases the range of concentration of duodenal contents was almost as wide as it was among the normal persons (Tables I, II and III). Little can be said about low values for only one specimen was examined in all cases in which such values were obtained. On the contrary, the high values obtained in certain cases showed that the changes found by the surgeon do not necessarily mean that such changes are associated with disturbance of external pancreatic secretion.

In eight of the cases the value for the serum lipase was normal. In the remaining two cases the value was high; in one case 3.5 cc. and in another case 8.3 cc. of twentieth-normal solution sodium hydroxide was required to neutralize the fatty acids liberated by 1 cc. of serum. It may be assumed from these values that any disturbance of pancreatic function secondary to the changes found by the surgeon had disappeared in eight cases but had persisted in two cases. It is interesting that in one of the two cases in which a disturbance of pancreatic function persisted, the duodenal contents contained no pancreatic enzymes, while in the other case the enzymes were present in normal amounts. In the last case, an acute disturbance of the pancreatic function (acute edematous pancreatitis) did not prevent the secretion of enzymes.

Chronic atrophic pancreatitis with steatorrhea. The concentration of pancreatic enzymes in the duodenal contents was studied in seven cases of chronic atrophic pancreatitis with steatorrhea. Pancreatic stones or pancreatic calcification was demonstrated roentgenologically in five of the seven cases. A pancreatic cyst was present in one case while diabetes mellitus was a complicating factor in two of the seven cases. Amylase was not demonstrated in the duodenal contents in any of the seven cases, although fifteen specimens were examined (Table I). Trypsin was demonstrated in only one case of the seven cases, in which fifteen specimens were tested (Table II) and in this case the concentration of trypsin in terms of grams of nitrogen per 100 cc. of duodenal contents was only 1.5 and 1.4 gm. Lipase was present, but only in very small quantities in the four cases in which the concentration of this enzyme was determined. Certainly there is a marked tendency to complete absence of enzymes in the duodenal contents in cases of chronic atrophic pancreatitis with steatorrhea. On the other hand, enzymes may be present in an adequate amount in cases of chronic pancreatitis with pancreatic stone but without steatorrhea. In one case not included in the tables the value for amylase was 4 gm. of d-glucose and the value for trypsin was 3.6 gm. of nitrogen per 100 cc. of duodenal contents.

Nontropical sprue. In the six cases of nontropical sprue, the concentration of amylase varied from 1.3 to 14 gm. of d-glucose per 100 cc. of duodenal contents (Table I), the concentration of trypsin varied from 1.7 to 9.4 gm. of nitrogen per 100 cc. of duodenal contents (Table II) and the concentration of lipase varied from 6 to 163 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents (Table III). In every case of nontropical sprue in this series, the duodenal contents contained enzymes in apparently adequate amounts. The constant presence of enzymes in these six cases was in contrast with the impression that enzymes are often absent in non-

tropical sprue. The regularity of occurrence of apparently adequate amounts of enzymes in the duodenal contents of patients with nontropical sprue also was in contrast with the regularity of their absence from the duodenal contents in cases of chronic pancreatitis with steatorrhea. Contrary to the opinions of some investigators, the examination of duodenal contents for pancreatic enzymes may be an important step in the differentiation of steatorrhea due to chronic atrophic pancreatitis and the steatorrhea of sprue, the two most important causes of steatorrhea.

SUMMARY AND CONCLUSIONS

The determination of the concentration of pancreatic enzymes in one or two samples of duodenal contents obtained in the manner described does not always give a satisfactory idea of the secretory capacity of the pancreas. In order to secure a satisfactory idea of secretory capacity of the pancreas, it is often necessary to examine not one but many samples.

The sample of duodenal contents chosen for analysis should probably be one as free as possible of gastric contents, but it need not contain bile. The concentrations of amylase, trypsin, and lipase in the duodenal contents usually run parallel, but this is not always the case.

Methods described by McClure, Wetmore and Reynolds for determination of the concentration of amylase and trypsin and the method of Crandall and Cherry for the determination of the concentration of lipase appeared to give results constant enough for clinical purposes. Among normal persons, the concentration of amylase varied from 1.3 to 15 gm. of d-glucose per 100 cc. of duodenal contents, the concentration of trypsin varied from 1.3 to 11.5 gm. of nitrogen per 100 cc. of duodenal contents, and the concentration of lipase varied from 3 to 179 cc. of twentieth-normal solution of sodium hydroxide per 1 cc. of duodenal contents. The range of concentration of pancreatic enzymes in the duodenal contents of normal persons is so wide that total absence of pancreatic enzymes alone may be taken as evidence of abnormal pancreatic function if pancreatic enzymes are absent from more than one specimen. The repeated finding of low concentrations may in all probability likewise be taken as evidence of diminished pancreatic function.

The range of the concentration of amylase, trypsin and lipase was practically normal in the presence of the following conditions: intrahepatic jaundice caused by cirrhosis or hepatitis, obstructive jaundice caused by a stone in, or a stricture of, the common bile duct, biliary disease which is associated with or a residuum of acute edematous pancreatitis, and nontropical sprue.

A marked contraction of the range of concentrations of amylase, trypsin, and lipase in the duodenal contents was found only in samples of duodenal contents taken from patients with carcinoma of the head of the pancreas, carcinoma of the ampulla of Vater, and chronic atrophic pancreatitis with steatorrhea. In cases of chronic pancreatitis without steatorrhea there was no remarkable contraction of the range of concentration.

The determination of the concentration of enzymes in the duodenal contents will aid in the localization of carcinoma obstructing the common bile duct when bile is not present in the duodenal contents. Absence of

both bile and enzymes from the duodenal contents localizes the carcinoma in the head of the pancreas or in the ampulla of Vater.

The constant finding of pancreatic enzymes in normal amounts in the duodenal contents in cases of

nontropical sprue and their almost constant absence in cases of chronic atrophic pancreatitis with steatorrhea is of considerable importance because it can help in the differentiation of these two most common types of steatorrhea.

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Relation of Constipation to Cancer

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SOME time ago Dr Friederick L. Hoffman, the noted medical statistician, pointed out to me the confused state of the literature regarding the possible part played by constipation in the causation of cancer. His far-reaching studies and his wide experience showed how difficult it was to reach a satisfying conclusion on the basis of the existing statistics. With his cooperation, a grant was secured through the generosity of Mr Samuel S. Fels of Philadelphia, for the purpose of studying this question by a critical review of personally controlled clinical material. The present report is the result of this study. It is a great pleasure, therefore, to acknowledge my appreciation of Dr Hoffman's stimulating encouragement which made possible the investigation here presented.

OBJECT

The purpose of this study is to determine the relation of cancer and constipation, and particularly whether constipation plays a demonstrable role in the etiology of cancer.

MATERIAL, METHODS, CRITERIA

The material used is an unselected list of 4,700 private patients complaining of digestive symptoms. These constitute a homogeneous group uniformly studied according to a standard routine procedure developed by the writer. The material is the same as that used for other clinical and statistical studies already published.

Constipation was diagnosed clinically according to the following criteria obtained from the history:

1. Complete failure of spontaneous bowel movements
 2. Laxation rate less than 6 stools per week.
 3. Severe cathartic, enema, or irrigation habit.
 4. Persistent difficulty in rectal emptying as evidenced by marked suppository or enema habit.
- In many cases where opportunity offered, the history was supplemented by roentgen determination of the total colon emptying time. The technic and

criteria of this particular type of observation have been published elsewhere (2).

In the general (unselected) series of 4,700 patients, the incidence of constipation was estimated at 54.2%.* It was considered important to separate from the total group of the constipation cases those recent cases which might have developed during the course of the malignant disease. Since it has been shown by Hoffman (3) that the "average" duration of carcinoma before the patient seeks medical advice may be set at 18 months, the line between long and short term constipation was drawn at this point. In other words, 3 groups of constipated patients were considered throughout this study, as follows:

- Group 1. Constipation of all durations.
- Group 2. Constipation of 1½ years duration or less.
- Group 3. Constipation over 1½ years in duration (1 minus 2).

In order to determine the incidence of "recent constipation," i.e. constipation lasting 1½ years or less, 200 consecutive cases of constipation were analyzed. In this group there were found 13 "recent" cases, an incidence of 6.5%. It was next necessary to calculate the incidence of "recent constipation" in the general or unselected series. This was done by multiplying the general incidence of constipation (54.2) by the factor 6.5 which gives the incidence of "recent constipation" in general as 3.5%. Conversely, the general incidence of constipation lasting over 1½ years was found to be almost 51% (100 — 6.5, or 93.5).

*Before beginning the present study the general incidence of constipation was actually determined in 4,443 histories. There were found to be 1,953 cases of constipation, an incidence of 44.2%. In the course of the study there were added as a result of intensive review of the case histories:

To 13 esophagus cases
To 20 rectal cases
To 101 stomach cases
To 45 colon cases

1 case of constipation
4 cases of constipation
9 cases of constipation
5 cases of constipation

179

Thus there were added 19 cases of constipation to the 179 cancer cases, an increase of about 10%. Maintaining this increase for the unselected list of 4,700 cases, the general incidence of constipation becomes 54.2%. This figure is, therefore, adopted as the corrected general incidence of constipation in the present study.

times 54.2%). These figures may be presented in tabular form as follows:

TABLE I

Incidence of constipation (in 4,700 unselected cases)

All durations	54.2%
One and one-half years or less (estimated from 200 cases)	3.5%
Over 1½ years (estimated from 200 cases)	50.6%

The criteria of cancer were those usually adopted in clinical studies, namely, characteristic roentgen appearance; results of operative exploration, autopsy or pathological section; and end result as determined by follow-up. All cases in which there was any doubt whatever, as to the diagnosis were excluded. In 2 cases of cancer of the bowel there was some question as to the location of the growth, whether in the pelvic colon or in the rectum proper. These were finally classified according to the best available evidence.

RESULTS

Cancer of the Esophagus. There were 14 cases. Constipation of all durations occurred in 6 or in 42%. Constipation over 1½ years in duration occurred in 4 or 28%. Thus the incidence of constipation is appreciably lower in cancer of the esophagus than in the general unselected series (51%). Details are presented in Table II.

TABLE II

Incidence of constipation in cancer of the esophagus (14 cases)

Constipation, all durations	in 6 cases or	42%
Constipation, 1½ years or less	in 2 cases or	14%
Constipation over 1½ years	in 4 cases or	28%
Constipation, none, or 1½ years or less	in 10 cases or	71%
Constipation, none	in 8 cases or	57%

Cancer of the Stomach. There were 101 cases. Constipation of all durations occurred in 53 or 52.4%. Constipation over 1½ years in duration occurred in 39 or 38.6%. Thus the incidence of constipation is lower in cancer of the stomach than in unselected patients (51%). Details are presented in Table III.

TABLE III

Incidence of constipation in cancer of the stomach (101 cases)

Constipation, all durations	in 53 or 52.4%
Constipation, 1½ years or less	in 14 or 13.8%
Constipation over 1½ years	in 39 or 38.6%
Constipation, none, or 1½ years or less	in 62 or 61.3%
Constipation, none	in 48 or 47.5%

Cancer of the Colon. There were 45 proven cases. Constipation of all durations occurred in 28 or 62%, or somewhat more frequently than in the general unselected series. However, constipation over 1½ years in duration occurred in only 19 or 42%, an incidence

appreciably lower than the basic figure of 51%. Details are presented in Table IV.

TABLE IV

Incidence of constipation in cancer of the colon (45 cases)

Constipation, all durations	in 28 or 62%
Constipation, 1½ years or less	in 9 or 20%
Constipation, over 1½ years	in 19 or 42%
Constipation, none, or 1½ years or less	in 26 or 57%
Constipation, none	in 17 or 37%

Cancer of the Rectum. There were twenty cases. Constipation of all durations occurred in 12 or 60%. Constipation over 1½ years in duration occurred in 10 or 50%, an incidence no higher than that in the general unselected series (51%). Details are presented in Table V.

TABLE V

Incidence of constipation in cancer of the rectum (20 cases)

Constipation, all durations	in 12 cases or 60%
Constipation, 1½ years or less	in 2 cases or 10%
Constipation, over 1½ years	in 10 cases or 50%
Constipation, none, or less than 1½ years	in 10 cases or 50%
Constipation, none	in 8 cases or 40%

DISCUSSION

Does Constipation Cause Cancer? The figures cited above give little if any support to the belief that pre-existing constipation plays any significant role in the etiology of digestive tract cancer. Summarizing the evidence, we find the following:

TABLE VI

Incidence of constipation in digestive tract cancer

	All durations	Over 1½ years
Esophagus	42%	28%
Stomach	52%	38%
Colon	62%	42%
Rectum	60%	50%
Average	54%	39.5%
In 4,700 unselected cases		
including non-cancer	54%	51%

In other words, the average incidence of constipation of all durations in cancer of the alimentary tract, all locations, is exactly the same as its incidence in an unselected series of 4,700 cases, namely 54%. However, the average incidence of long standing constipation in cancer is distinctly less than in the general series.

Does Cancer Cause Constipation? On the other hand, there is positive evidence that cancer may be regarded as a cause of constipation. In this connection it should be appreciated that the interval used in this study to indicate the duration of cancer before medical advice is sought (1½ years) is probably very conservative. As a matter of fact, no one yet knows how long cancer may exist in the body without giving localizing evidence of its presence, much less without causing general or remote symptoms, such as consti-

pation, which may readily be overlooked or taken for granted by the patient. At any rate, cases of digestive malignancy have been known to exist much longer than 1½ years. Thus Pfahler (4) has recently reported a case of stomach cancer which lasted for 7 years without giving rise to gastric symptoms.

If we restrict our attention to the arbitrary 1½ year period mentioned above, we find from analysis of our material, the following:

TABLE VII

Development of constipation in digestive cancer in the 1½ years preceding medical observation ("recent constipation")

In esophageal cancer recent constipation occurred in	14%
In gastric cancer recent constipation occurred in	14%
In colonic cancer recent constipation occurred in	20%
In rectal cancer recent constipation occurred in	10%
Average in all cancers recent constipation occurred in	14.5%
In the general series recent constipation occurred in	3.5%

In other words, it seems safe to conclude that cancer of the alimentary tract, regardless of location, is a cause of constipation in about 14.5% of patients previously free from this type of bowel malfunction. This is about 4 times its frequency in unselected cases. It should be repeated that these figures are on the conservative side because: (1) They do not take into account those patients previously constipated in whom constipation was increased in severity during the interval under discussion; (2) they do not include possible cases in which constipation came on for the first time as a result of cancer existing longer than 1½ years.

The thesis that constipation is the result of cancer is also supported independently by a scrutiny of unselected constipation cases. As a matter of fact, it is rare for constipation to develop recently, i.e. within 1½ years of the time of seeking medical aid. In the majority of cases constipation is a life-long condition beginning during the youth or childhood of an individual. A comparison of the incidence of "recent constipation" in non-cancerous and in cancerous individuals is shown in Table VIII.

Hence it appears that "recent constipation" is at least 5 times as common in cancerous as in non-cancerous cases.

Relation of Site of Cancer to Constipation. It is interesting to observe that the incidence of constipation apparently increases as one follows the course of carcinoma from the proximal to the distal portions of the alimentary canal. This is apparent from a con-

sideration of Table VI, in which the site of cancer is presented in anatomical order.

The explanation of this phenomenon may possibly reside in the fact that the nearer the growth is located to the end of the alimentary tract the greater the interference with normal bowel evacuation.

TABLE VIII

Relation of "recent constipation" to constipation of all durations in cancerous and non-cancerous patients

In non-selected constipated cases recent constipation occurred in	6.5%
In non-cancerous constipated cases recent constipation occurred in	5.0%*
In all constipated digestive cancer cases recent constipation occurred in	27.0%
In constipated cancer of esophagus cases recent constipation occurred in	33.0%
In constipated cancer of stomach cases recent constipation occurred in	26.0%
In constipated cancer of colon cases recent constipation occurred in	32.0%
In constipated cancer of rectum cases recent constipation occurred in	17.0%

*Of the 13 "recent" cases encountered in the 200 constipated patients used in preliminary review (Table I), 10 were non-cancerous, giving the above incidence of 5 per cent.

SUMMARY

1. One hundred and seventy-nine cases of cancer involving the esophagus, stomach, colon, and rectum were analyzed for the incidence of constipation. The resulting findings were compared with a similar analysis of 4,700 unselected patients suffering from various digestive disorders.

2. Constipation of all durations occurred on the average as frequently in the cancer cases as in the general series.

3. Constipation of 1½ years duration or less ("recent constipation") was relatively much more frequent in the cancer cases than in the general series.

4. Accordingly, there is no evidence that constipation is the cause of digestive tract cancer.

5. Conversely, there is evidence that digestive tract cancer causes constipation.

6. The incidence of constipation increases as one follows the course of cancer from the proximal to the distal portion of the alimentary canal.

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Chronic Regional Enteritis Occurring in Three Siblings

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SEARCH of the literature as far back as 1806 reveals reports of cases of disease of the small intestine of a type which, since 1932, we have noted to be apparently of increasing frequency. This disease we now classify under the clinicopathologic term either of "regional enteritis" or "enterocolitis."

Several clinical features of thrombo-ulcerative colitis and of regional enteritis are similar but there is one manifestation which is distinctly characteristic of each. Colitis does not invade the small bowel except as a late complication of a seriously progressive disease and, in turn, regional enteritis originates in the small bowel and only as it progresses does it extend into the colon. We have frequently observed extensive enterocolitis (lower part of the ileum and right portion of the colon) at operation, at which time an ileocolonic stoma has been established. A few weeks later, when resection of the ileocecal coil has been undertaken, the disease in the colon has disappeared, although the terminal portion of the ileum has retained all the characteristics of chronic, regional enteritis. The disease may progress throughout the colon but it is our belief that its primary focus is in the small intestine. Hence, regional enteritis would appear to be the first, and enterocolitis the second, step in the evolution of this unusual process of unknown etiology.

Another unique feature of either colitis or enteritis is the rarity of its occurrence in more than one member of a family. Among some 2,500 patients with chronic ulcerative colitis seen at The Mayo Clinic, there were only about fifteen familial pairs; that is, a parent and a child, or two siblings. Crohn (2) reported regional enteritis as afflicting two sisters. Our report deals with regional enteritis affecting two sisters and one brother of a Jewish family. Moreover, a second brother has a bowel disturbance which possesses many features in common with the disturbance affecting the others but an examination of his colon and ileum has not been obtained.

Of additional interest is the fact that the three siblings represent three phases of regional enteritis. In Case 1 the condition was limited to the terminal portion of the ileum. In Case 2 the terminal portion of the ileum and the cecum, and later, multiple areas in the small bowel were involved. In Case 3, the terminal portion of the ileum was affected and there was also irregular but extensive involvement of the colon as far as the splenic flexure. Reports of the three cases follow:

REPORT OF CASES

Case 1. The brother of the two women was aged thirty-five years when he came to the clinic in 1933, at which

time an anal fistula was treated by operation. No diarrhea or constipation was noted at that time. In 1937, he was subjected to much worry and nervous tension due to business reverses and he began to have diarrhea with passage of about six stools a day. The stools were loose and watery; they contained no blood or pus but their passage often was accompanied by a cramping feeling across the lower portion of the abdomen, mostly on the right side. Gas and a sensation of fullness also were noted and appeared about two hours after eating. The man would often feel a "knot" in the right lower quadrant of the abdomen; this sensation was relieved by the passing of loose fecal material. On many days only loose stools were noted. The drinking of cold water would increase the distress and diarrhea. The patient always ate hurriedly and was of a highly nervous temperament.

Physical examination disclosed no abnormality. Results of studies of the blood were negative. Other than to demonstrate the presence of mild pruritus, anal and proctoscopic examination gave negative results. Roentgenologic examination, following barium enema, revealed ulcerative hyperplastic ileitis involving about 15 inches (37 cm.) of the terminal portion of the ileum (Fig. 1). Ileocolostomy, with resection of the diseased portions, was advised but the patient was not prepared to remain.

Comment on Case 1. This case illustrates the uncomplicated type of regional enteritis which involves only the terminal portion of the ileum. The disease appeared to be sharply limited to this segment and the patient presumably would have been cured by ileocolostomy and resection. He was strongly urged not to delay surgical intervention, because the danger of delay had been so well illustrated by the cases of his sisters, as will be seen. Another feature in his case was the association of emotional stress with the onset of his bowel symptoms. We do not think that nervous and psychic trauma actually cause inflammation of either the small or large bowel, but since nervous and psychic trauma so frequently accompany this type of intestinal inflammation, we feel that they may well be contributing factors.

Case 2. One sister, aged twenty-two years, when she was first examined at the clinic, had enjoyed good health until 1928, when frequent loose stools had been noted. Diarrhea had persisted at intervals until 1931, when marked diarrhea developed, associated with postprandial distress and cramping pains throughout the lower part of the abdomen. Blood or pus had not been noted in the stools. The patient's illness had persisted and she became weak. Anorexia, loss of weight and insomnia had been prominent complaints. She had noted some tenderness of the right side and in January, 1932, her appendix had been removed. The patient said that the surgeon had reported the appendix to be involved by tuberculosis. Although the incision had healed promptly, the operation seemed only to increase the severity of the symptoms.

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Fig. 1. Anteroposterior roentgenogram, made on December 8, 1938, of the colon of a male, thirty-five years old, having ulcerative, hyperplastic ileitis involving approximately 15 inches of the terminal portion of the ileum, which is visualized here only with difficulty as it joins the cecum from below and on the posterior aspect of the cecum.

When first seen at the clinic in May, 1932, the woman was passing four to five watery stools a day, accompanied by much gas and cramping pains in the lower portion of the abdomen. Her weight had diminished from 130 to 85 pounds (59 to 39 kg.). She had a low grade fever, her temperature being approximately 99.8° F. Her skin was dry and scaling. In the lower right quadrant of the abdomen a rather soft, tender mass was palpable. Moderate edema extended half-way to her knees.

The concentration of hemoglobin was 12.2 gm. per 100 cc. of blood; erythrocytes numbered 4,420,000, and leukocytes 10,900 per cubic millimeter; and the differential count was normal. The concentration of total gastric acids was 58 units, and of free hydrochloric acid, 30 units (Töpfer's method). The stools were negative for parasites and ova. The only abnormality revealed at proctoscopy was an anal fissure. The presence of an old, healed, right apical tuberculous lesion was found roentgenologically. Roentgenologic examination following a barium enema disclosed that the tip of the cecum and the terminal portion of the ileum were involved in a mass of pericecal adhesions (Fig. 2a). The distal portion of the colon was normal.

A tentative diagnosis of ileocecal tuberculosis was made and surgical intervention was undertaken on May 31, 1932. The terminal portion of the ileum was found to be thickened and joined to an infiltrated and adherent cecum. End-to-side, ileotransverse colostomy was done with the intent of resecting the involved portion later. The patient made a good recovery and was sent home on June 18, 1932, at which time she was passing only two stools a day and was experiencing no pain. She remained well and gained 40 pounds (18 kg.). But in June, 1933, shortly before being married, she complained of a sensation of fullness

in the abdomen, of gas and diarrhea and of loss of 15 pounds (7 kg.).

The woman returned to the clinic in May, 1935. A roentgenogram of the colon, made at this time, disclosed only slight deformity of the tip of the cecum. She was instructed to follow a low residue diet and a life as free from strain as possible, and she was given tincture of iodine and dihydranol to take by mouth. She maintained fairly good health until January, 1936, when diarrhea re-occurred along with much gas, anorexia, severe abdominal cramps, foul, fatty stools, loss of weight and strength and occasional fever. Again no blood was noted in the stools. The symptoms increased in severity until the patient returned to the clinic in October of 1936. At that time she weighed 98 pounds (44 kg.) and appeared to be seriously ill. Loud peristaltic sounds could be heard and the abdomen was distended by dilated loops of intestine. Examination following a barium enema revealed persistence of the slight deformity of the tip of the cecum and loss of distinctness of the mucosal pattern about the ileocolonic stoma (Fig. 2b).

Surgical exploration was carried out on November 2, 1936. The terminal portion of the ileum, which had been left with an inverted stump, had shrunk to about a third its normal size. In the ileum were many thickened, edematous partially obstructing processes due to localized inflammation; dilatation and thickening were present in segments proximal to the obstructed portions. The portion of the ileum which was diseased was larger than the portion which was normal. At the distal end of the jejunum there was a large, inflammatory mass involving 4 inches (10 cm.) of this portion of the bowel, above which the bowel was markedly dilated. Enterostomy was performed, joining the jejunum to the ileum around this mass. The ileum, which showed evidence of twisting at the ileocolonic stoma, was sutured for 5 inches (13 cm.) to the transverse colon and parallel with it. The patient made a good recovery and was dismissed from the hospital eighteen days after operation, experiencing only occasional cramping pain and passing two or three stools a day. She returned home with instructions to take dysentery vaccine made from the Flexner and Sonne-Duval strains of bacilli, because her blood serum had weakly agglutinated these strains. When we heard from her in November, 1938, she weighed 128 pounds (58 kg.) and felt well. At this writing she was six months pregnant and stated that her bowel movements were more regular than at any other time of her life.

Comment on Case 2. Crohn, Ginzburg and Oppenheimer (1) presented their description of this disease in May, 1932, and it was published in October. Conditions found at surgical operation at the clinic convinced us that tuberculosis was not the cause of the disorder; this patient was one of a gradually increasing group whose correct classification seemed established by the report of the investigators named. In retrospect, and with increased knowledge, we now wish that the terminal portion of the ileum and the right portion of the colon had been resected not later than at the patient's second visit to the clinic in June, 1933. Surely she was having an exacerbation of the condition, but of course, no one knows if there were then early areas of enteritis in the ileum proximal to the site of the ileostomy. Moreover, the severing of the ileum for the anastomosis precluded any satisfactory check as to the status of its terminal segment. At the time of the woman's third examination, in November, 1936, she was almost as ill as she had been when we first had seen her in 1932. Operation in 1936 disclosed such extensive damage to the ileum that we had little hope for her improvement. It is amazing

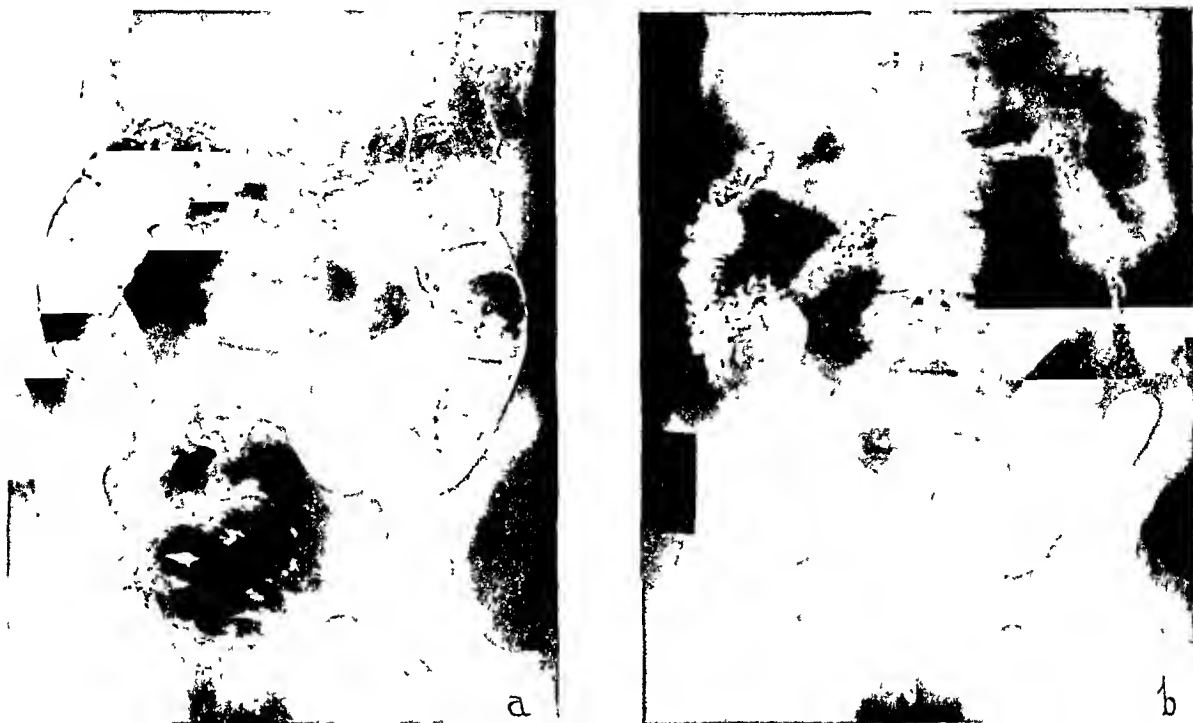


Fig. 2a. Anteroposterior roentgenogram, made on May 26, 1932, of the colon of a female, twenty-two years old (sister to the male of Fig. 1), in which the cecum and the terminal portion of the ileum are seen to be involved by inflammatory disease. Periceecal adhesions are present about the tip of the cecum and the terminal portion of the ileum; but that portion of the colon distal to the cecum is normal; b, anteroposterior roentgenogram of the same patient, made on October 7, 1938. The mucosal pattern of the site at which an end-to-end ileotransverse colostomy was performed in 1932 is seen here to be indistinct. The tip of the cecum still exhibits the same deformity that had been observed previously.

and gratifying to us to know how well she has been since then. Whether or not the strain of pregnancy will cause an exacerbation cannot be foretold, but the danger is obviously considerable. The ultimate prognosis in cases of extensive regional enteritis is unfavorable (3).

Case 3. The second sister, aged twenty-four years, was examined at the clinic on May 25, 1932. As in her sister's case, abdominal distress had developed and finally she had been operated on in 1929. A diagnosis of acute appendicitis had been made. The wound healed well but diarrhea developed; she passed eight to ten loose, watery stools a day and had cramps, gas and abdominal distress. She had not seen blood in the stools. She suffered from marked anorexia and weakness. Treatment for chronic ulcerative colitis had been instituted by her physician at home. Her weight declined from her norm of 125 pounds to 67 pounds (57 to 30 kg.) in the following six months. Under treatment with serum and general measures, she had been able to resume work by February, 1930. She had gradually gained until she weighed 108 pounds (49 kg.) when she came to the clinic in May, 1932. At that time, she complained of fatigue, weakness and urgency of defecation, especially after the noon meal. There was an associated, indefinite abdominal distress.

On physical examination she appeared undernourished, high-strung and nervous. There was slight tenderness over the lower portion of the abdomen.

Examination of the blood disclosed the following: Concentration of hemoglobin, 12.3 gm. per 100 cc.; erythrocytes, 4,640,000 and leukocytes 7,800 per cubic millimeter; differential count, normal. Proctoscopic examination disclosed two rectal polyps and hemorrhoids. Roentgenologic

examination of the thorax gave a negative result but that of the colon following a barium enema disclosed a filling defect immediately proximal to the hepatic flexure (Fig. 3a).

In view of the lesion in the ascending colon, operation was performed on June 3, 1932. The colon and the terminal portion of the ileum were seen to be contracted, inflamed and covered with a thin exudate. The mes-enteric was thickened at the ileocecal coil. The colon was apparently normal between the cecum and the lesion at the hepatic flexure.

The surgeon commented that the bowel had the appearance of being involved by chronic ulcerative colitis or by diffuse polyposis in association with much infection. The abdomen was closed after exploration only. The post-operative course was uneventful and the patient was dismissed on June 18. At that time, she was passing only two stools a day. She was given vaccine for ulcerative colitis, to be administered at home. Recovery was rapid and by the spring of 1937 she weighed 118 pounds (53 kg.). During this interval she was passing two soft stools daily, and only occasionally did she experience cramping pains or diarrhea. In the spring of 1937 severe bronchitis developed and was followed by diarrhea with passage of about six stools a day. This diarrhea soon subsided.

In July, 1937, the patient became pregnant and during the succeeding nine months was ill with diarrhea; sharp, colicky, abdominal pain occurred with passage of the stools and also after meals. Because of her poor general condition, she was delivered by cesarean section in April, 1938. Following delivery, she was bedridden. Diarrhea, with passage of from eight to ten stools daily, continued but no blood or pus was noted on gross inspection. Her



Fig. 3a. Anteroposterior roentgenogram, made on May 28, 1938, of the colon of a female, twenty-four years old (sister to the female of Figs. 2a and 2b and the male of Fig. 1), showing a filling defect revealed by the contrast medium in the colon immediately proximal to the hepatic flexure; b, anteroposterior roentgenogram of the same patient, made on December 3, 1938, showing extensive ileocolitis with hyperplastic changes, involving the lower 8 to 10 inches of the ileum, and the ascending and transverse portions of the colon to the sigmoid. The cecum and that portion of the colon distal to it, however, exhibit no evidences of involvement.

weight diminished to 79 pounds (36 kg.). She returned to the clinic on November 9, 1938. Her skin was dry and scaling, her tongue was red and smooth, and there was marked inflammation and excoriation about the anus and vulva. Examination of the abdomen disclosed much tenderness in the right lower quadrant. The anus was greatly contracted, which made proctoscopic examination painful, but the rectal mucosa was normal as far as it could be seen (about 20 cm.). The roentgenogram of the colon made on December 3, 1938, disclosed extensive ileocolitis with hyperplastic changes which involved the lower 8 to 10 inches (20 to 25 cm.) of the ileum and the ascending and transverse colon (Fig. 3b). The cecum and the distal portion of the colon were involved little, if any. There was moderate anemia. Results of the tuberculin skin test, which was done with purified protein derivative, were negative. A diagnosis of regional enteritis with extension to the colon was made and hospitalization was advised.

She was given a transfusion of 500 cc. of whole blood. A high protein, low residue diet, supplemented with Vitamins B₁, B₂, and nicotinic acid, administered both orally and parenterally, was prescribed. The condition of the tongue and mucous membranes improved rapidly and the number of stools was decreased to three and four a day. Abdominal cramps persisted and the patient's appetite was capricious. Administration of neoprontosil in doses of 60 grains (4 gm.) a day was started on December 4 and continued to December 12, 1938. A perirectal abscess ruptured into the rectum on December 10, and drainage had continued to the time of writing. The improvement was definite, but so slow that it seemed wise to allow her to continue convalescence at her home, in the hope that she might recover. She was directed to continue to eat as much as possible, to take the Vitamin B₁ daily and to receive intermittent ten-day courses of neoprontosil. If she

improved it was planned to perform ileosigmoidostomy, which was to be followed by resection of the colon and the terminal portion of the ileum.

Comment. The cases of both sisters demonstrate what extreme loss of weight and deficiency may occur—Case 2 represents a loss of weight from 130 to 85 pounds (59 to 39 kg.); Case 3, from 125 to 67 pounds (57 to 30 kg.). Likewise, both sisters had been subjected to appendectomy and yet the true condition was not recognized. It is understood that regional enteritis as a definite entity was not generally diagnosed as such until 1932.

At the operation performed in May, 1932, the second sister (Case 3) had such extensive disease of the colon and terminal portion of the ileum that surgical treatment was not possible. The filling defect in the ascending colon was caused by thickening and inflammation in that region. How or why she should improve after the exploration cannot be said. Exacerbations of the disease initiated by the strain of an intercurrent respiratory infection and also of pregnancy are common.

When we saw the patient (Case 3) in November, 1938, she was seriously ill and much depleted. The various indications of a multiple deficiency state prompted the administration of large doses of Vitamins B₁ and B₂ or G. The marked anal and vulvar irritation improved but little until she received a six-day course of from 150 to 200 mg. daily of nicotinic acid. As full and as liberal a diet as she could tolerate was prescribed, emphasizing the inclusion of fresh

meats. Improvement was slow and when this paper was written there was no immediate prospect that operation would be performed. Hence, it was hoped that a period at home might hasten her improvement. In this case, as far as could be determined from the roentgenogram, the disease extended from the terminal portion of the ileum to the splenic flexure of the colon. If this is correct, there is reason to hope that a remission may ensue. If such occurs, the surgeon may be able to effect a shunt, so to speak, around the diseased portions, as well as to resect the segment affected by enterocolitis.

SUMMARY

Three siblings, two sisters and a brother, have been found to exhibit various manifestations characteristic

of regional enteritis. The occurrence of this disease in three members of one family is uncommon. The great difficulties that may arise in the management of this disease are illustrated by the cases of the sisters. In the light of present knowledge, resection of the diseased portion is the therapeutic procedure of choice but a better understanding of this unusual disease may, in the future, offer a less radical treatment. We feel that enterocolitis is a late stage in the progress of regional enteritis.

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Gastric Secretion in Extragastic Malignancy*

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THE diminution in gastric secretion which occurs in cases of gastric malignancy has long been recognized. Evidence has also been produced on several occasions which suggests that a similar reduction in stomach secretion is found in patients with extragastric malignancy. Fenwick (1) in 1880 made careful histologic studies of the gastric mucosa in a series of cases of carcinoma of the breast and uterus, and in many of these found marked atrophy of the gastric mucosa. Ewald (2) reported gastric anacidity and mucosal atrophy in a patient with a carcinoma of the duodenum situated 2 cms. below the pylorus. The anacidity and mucosal atrophy in this case were probably due to pyloric occlusion or pyloric spasm and gastritis. Moore, Alexander, Kelly and Roaf (3) in 1905 investigated 17 patients with "malignant disease of organs other than the stomach." They concluded that "the absence of free hydrochloric acid in cancer of the stomach is not due to local action in that organ, for hydrochloric acid is absent or reduced greatly in amount whatever may be the situation in the body of the growth." Riegel (4) observed lowered gastric acidity in cases of carcinoma of the esophagus. Friedenwald and his collaborators (5 and 6) carefully investigated gastric secretion in patients with extragastric malignancies. In a large proportion of these cases they found lowered gastric acidity which persisted "even after removal of the cancerous mass."

If this lowered gastric acidity in association with extragastric malignancy actually does occur, it would

be of considerable significance for two main reasons. First the reduction in acid content of the stomach secretion would serve as a useful diagnostic aid in questionable cases of malignancy, and secondly, it might reveal a hitherto unknown relationship between gastric secretion and malignant growths.

It was for the purpose of determining experimentally if extragastric carcinomas are accompanied by impaired gastric secretion that this investigation was undertaken.

MATERIAL AND METHODS

The determinations were carried out on rabbits which had been inoculated with the Brown-Pearce rabbit carcinoma.[†] The latter is a highly malignant carcinoma of the testis which metastasizes extensively and rapidly produces a diffuse carcinomatosis. Tumors were also transplanted into the anterior chambers of rabbit's eyes and suspensions of tumor cells were inoculated intravenously. In all, 16 tumor rabbits were used, 14 of which had bilateral primary testicular tumors with extensive metastases to all the thoracic and abdominal viscera, one had a large tumor of the eye, and one had been inoculated intravenously with a suspension of tumor cells producing an overwhelming carcinomatosis. In order to ensure a more fulminating carcinomatosis the animals were also treated with 1:2:5:6-dibenzanthracene as described in a previous communication (7).

In order to determine the normal values for gastric

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[†]This tumor was supplied through the courtesy of Dr. J. B. Murphy of the Rockefeller Institute for Medical Research.

acidity and pepsin in our rabbits gastric analyses were done on 5 normal rabbits.

Gastric analyses were also done on two rabbits receiving injections with 1:2:5:6-dibenzanthracene to determine whether or not this substance might affect gastric secretion.

The determinations were done twice weekly. The animals were starved for 24 hours before aspiration

and for pepsin 8.30. Only in an occasional tumor animal did the gastric acidity values fall below this level, the average values for all the tumor animals being higher than this level (Table II), the average free acid being 80, the total acid 153 and the pepsin 5.42. In tumor rabbit No. 13 the free acid dropped to 24 and the total acid to 85. However, as was proven at autopsy one day after the first aspiration, this

TABLE I
Average values for gastric secretion in each animal

Rabbit No.	CONTROLS					TUMOR RABBITS																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
No. of gastric aspirations	5	2	6	3	3	4	2	4	6	1	1	1	5	5	2	2	4	1	5	3	1		
Free acid	104	13	86	89	76	67	96	87	66	55	24	148	103	96	145	66	59	127	71	88	76		
Total acid	125	40	129	163	146	125	157	134	96	73	85	198	158	156	189	135	121	167	112	133	111		
Pepsin	11.21	6.78	3.96	6.27	13.28	8.58	.93	2.60	7.10	3.66	26.83	2.82	10	4.30	3.89	2.21	9.88	3.72	3.87	2.16	4.65		

in order to obtain partial evacuation of the stomach without which gastric juice could not be aspirated. The technique of aspiration was as follows: A No. 16 urethral catheter was slowly passed over the rabbit's tongue, the forefinger of the operator's hand being kept in the animal's mouth between the jaws, thus compelling the animal to perform chewing movements. In this manner the tube was directed down the esophagus and prevented from entering the trachea. Five to ten ccms. of gastric juice could usually be aspirated without great difficulty. The gastric juice was titrated for free and total acidity using Töpfer's reagent, phenolphthalein and N/10 sodium hydroxide. The values for acidity are expressed in clinical units, i.e. ccms. of N/10 HCl in 100 ccms. of gastric juice. Pepsin determinations were done by the modified Mett method (8). Pepsin values are expressed in Mett units, i.e. in squares of the average digestion of the Mett tubes.

Careful histologic studies of the gastric mucosa were also done in several of the tumor animals to determine if any mucosal atrophy occurred as described by Fenwick (1).

RESULTS

A few of the animals did not tolerate the aspiration procedures well and died, usually of a bronchopneumonia following the first or second aspiration. In most of the rabbits, however, it was possible to obtain at least four or five samples of gastric juice before the animals succumbed to the effects of the carcinomatosis, cachexia and usually a terminal bronchopneumonia. At autopsy an extensive spread of the carcinoma to lungs, liver, spleen, kidneys, lymph nodes and other organs was found in all the tumor animals. The average duration of life following the first appearance of the tumor was usually three to five weeks.

An analysis of Table I shows essentially that there is very little variation in gastric secretion between normal animals and cancer animals. In only an occasional rabbit was there any reduction in gastric acidity. Even in those animals which died with marked cachexia and extensive carcinomatosis normal values for free and total acid and for pepsin were obtained in nearly all cases. In the normal animals the average value for free acid was 74, for total acid 121,

rabbit had a bilateral bronchopneumonia and was extremely cachectic in addition to having a diffuse carcinomatosis at the time the gastric juice was obtained. It is an established fact that a severe infection with high fever such as a bronchopneumonia will cause a reduction in gastric acidity. This is further substantiated by the fact that control rabbit No. 2, without tumor growth had low levels for gastric acidity (free acid 13, total acid 40) and at autopsy following the second aspiration was also found to have a bilateral confluent bronchopneumonia. Even tumor rabbit No. 23, which had been inoculated intravenously with a suspension of tumor cells and which at autopsy was

TABLE II
Average values for gastric secretion in the series of normal rabbits and in the series of rabbits with extragastric carcinoma

	Controls	Tumor Rabbits
Number of rabbits	5	16
Total number of gastric aspirations	19	47
Free acid	74	80
Total acid	121	153
Pepsin	8.30	5.42

found to have hundreds of tumor nodules scattered throughout the various organs, had a free acidity of 76 and a total acidity of 111.

Confirming various authors we noted that in those animals with low gastric acidity the pepsin values were elevated, and that in animals with high acidity values for pepsin were diminished.

In the two normal rabbits treated with 1:2:5:6-dibenzanthracene to determine whether this substance might affect gastric acidity no essential changes in gastric secretion were observed.

Histologic studies of the gastric mucosa of rabbits with diffuse carcinomatosis failed to reveal any evi-

dence of mucosal atrophy as reported by Fenwick (1). All of the tumor rabbits developed a moderate secondary anemia, the hemoglobin levels ranging from 60%-75%, and the red blood cell count from 4,000,000-5,000,000.

DISCUSSION

The above described experiments provide fairly conclusive evidence that in rabbits the secretion of the stomach is not affected by extragastric malignant tumors. In only one of the tumor rabbits (No. 11) was a progressive drop in the free and total acid content of the gastric juice noted, but as mentioned above this animal had a bilateral bronchopneumonia at the time the gastric secretion was obtained. The reduction in gastric acidity in this case was probably due to the overwhelming infection and fever. In a few of the other tumor rabbits occasional low acid values were observed, but they invariably returned to normal levels even though the tumors continued to grow progressively and the animals became more and more cachectic.

If we are to apply these results to man the conclusions described by the authors mentioned above must be doubted; this is supported by observations of other authors: Comfort, Butsch and Eusterman (9) studied gastric acidity in 89 patients before and after the development of carcinoma of the stomach. The gastric acidity was low in 79 of these subjects before gastric carcinoma developed; a number of these cases were investigated many years before the malignancy appeared. Another important fact which must be considered in evaluating the results obtained by the earlier investigators is the well known observation that in the age group in which malignant growths usually appear a high incidence of hypoacidity or anacidity is found in a normal population. In the series of cases described by Friedenwald and Rosenthal (6) of the 29 patients, 13 were males ranging in age between 42-69 with an average age of 54, and 16 were females whose ages ranged between 38-62 years with an average age of 52 years. According to a statistical study made on a vast number of subjects

by Vanzant, Alvarez, Eusterman, Dunn and Berkson (10), the percentage of true and apparent achlorhydria in males between 50-54 is 19.5% and 18.5% respectively and in women it is 22.8% and 15.8% respectively. These authors also showed that in man the free and total acid diminish considerably with advancing age. It is apparent therefore that in the relatively small series of cases reported by Friedenwald and Rosenthal the authors are not justified in ascribing the reduced gastric acidity to the malignant growths since most of their patients fall into the age group in which achlorhydria is fairly common in normal individuals.

SUMMARY AND CONCLUSIONS

Gastric secretion was investigated in a series of 16 rabbits with Brown-Pearce tumors in an attempt to substantiate the clinical observation that human beings with extragastric malignancies have diminished gastric acidity. No alteration in gastric acidity or pepsin was observed even in animals with extensive carcinomatosis.

These findings together with the observation that diminished gastric acidity may be present long before the appearance of a malignant tumor, and the fact that a higher incidence of achlorhydria and diminished gastric acidity occur normally with advancing age lead to the conclusion that reduced acid secretion in the stomach in cases of extragastric malignancy has not been established beyond doubt.

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The Gastro-Intestinal Onset of Pulmonary Tuberculosis*

By

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THE onset of pulmonary tuberculosis is extremely variable. At times it fails to be recognized by both patient and physician. Tuberculosis is a disease of many manifestations. Like syphilis, it may masquerade as other ailments. Seldom does it affect two persons in exactly the same manner. Even when two individuals of the same age, sex, and approximate station in life develop pulmonary tuberculosis of the same lung area, nevertheless their respective clinical courses may be entirely different. One of them may have a normal temperature, the other has a fever; one

carries on his work, the other is bed-fast; one lives, the other dies.

W. G. Brown (1), a lay victim of tuberculosis, was writing his "Confessions of a T. B." in 1914, when he was interrupted by the Grim Reaper before he could complete his task. His unfinished manuscript appeared posthumously in the Atlantic Monthly in which he describes his "initiation into the brotherhood of the T. B.s."

"A word about the way we enter it," he wrote, "of the initiation into our brotherhood. Unfortunately it is not always the same. On the contrary, the entrances are innumerable, however sole the exit. Indeed the

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initiation varies so widely that one would not be far wrong in saying that it is never the same twice. Yet many initiations have certain features in common, and in a general way it may be said that all belong to one of two great classes, the sudden and the protracted."

Most writers agree with this general classification of the onset of pulmonary tuberculosis, namely, the sudden and the protracted.

The sudden onset is the less common form. An example of it occurs in the patient who has heretofore considered himself in the best of health, when suddenly without apparent warning feels a warm sensation in his throat and brings up a mouthful of blood.

The protracted onset is the more common form. Usually it begins with a cold, the same sort of cold that the patient has had for several winters; but whereas the cold has previously subsided under some favorite remedy, this time the cold persists in spite of the best efforts to dislodge it. Instead it is followed by the appearance of flushes, fever, fatigue, sputum, loss of weight and other symptoms which direct attention to the lungs, and examination discloses the tuberculous nature of the ailment.

The protracted is the common form of the "initiation into T.B. . . yet the entrances are innumerable." Fishberg (2) states that the onset may at times suggest cardiovascular disease, anemias, menstrual disorders, dyspepsias or neurasthenias. "In many patients," he writes, "the gastro-intestinal symptoms are so pronounced that they completely mask the underlying pulmonary nature of the disease, and the patient may be treated for 'stomach trouble' for some time before the true nature of the disease is uncovered."

Our attention was directed to the gastro-intestinal onset of pulmonary tuberculosis by a patient who complained of dyspepsia, nausea and vomiting for a number of years. During this time there was never any suggestive pulmonary involvement beyond the usual winter colds. Her tuberculosis was accidentally uncovered during a routine school examination when she was found to have a positive tuberculin test, which later was shown to be a manifestation of an active pulmonary tuberculosis. Under sanatorium treatment for the tuberculosis, the digestive symptoms completely subsided.

Case 1. Gastro-Intestinal Onset of Pulmonary Tuberculosis.

K. E., a girl of sixteen, had been troubled with attacks of dyspepsia for several years. These would begin commonly after the evening meal or if she overloaded her stomach. A disagreeable feeling manifested itself in the upper abdomen accompanied by nausea and sometimes vomiting. These spells would last for five to ten minutes and then subside. For some time afterwards she would lose her appetite for food, also she would lose a few pounds in weight, which she would regain later with the return of the appetite. The attacks occurred once a month.

Aside from these dyspepsia attacks, she had enjoyed good health, with the exception of the usual diseases of childhood and occasional winter colds from which she always promptly recovered.

During a routine school examination she was found to have a positive tuberculin test. She had no knowledge of any lung trouble. She had had no cough, no sputum, no pains in the chest, no night sweats, no flushes, her temperature had not been taken so she did not know if she had a fever.

Physical examination showed a well nourished girl weighing 121 pounds, measuring 5 feet 2 inches in height. Her temperature was 99, her pulse 94, her respiration 20. The cervical glands were not enlarged.

The chest expansion was good. The left lung had good resonance. There were no rales and no rubs. The right lung had impaired resonance down to the fourth rib with bronchovesicular breath sounds and some dry clicking rales in this area.

The heart, abdomen and reflexes were approximately normal.

The urine was normal. The blood showed a slight secondary anemia. The sputum contained no tubercle bacilli, however, tubercle bacilli were found in the gastric contents.

The films of the chest showed extensive fibrotic changes in the right lung involving the apex, first and second interspaces, combined with scattered small calcified nodules. Both hili were accentuated. There was present marked peribronchial thickening bilaterally especially on the right side. The right side of the diaphragm was somewhat elevated. The heart outline was normal.

A diagnosis was made of active pulmonary tuberculosis. The patient was hospitalized and given routine sanatorium treatment.

The digestive symptoms subsided rapidly, the appetite improved, the bowel function became normal and there were no more attacks of dyspepsia. In the following six months, there had been no recurrences of the digestive symptoms, although there was an increase in the pulmonary tuberculosis requiring the induction of pneumothorax of the right lung.

In this case, patient K. E. apparently manifested the gastro-intestinal onset of pulmonary tuberculosis. When sanatorium care was instituted for the pulmonary tuberculosis the digestive symptoms subsided. No special attention had been directed at the dyspepsia. Apparently the digestive onset was a gastro-intestinal expression of the pulmonary tuberculosis.

Commenting on the subject of patients with pulmonary tuberculosis who present essentially gastro-intestinal symptoms, Gaither (3) states that, "Not a year passes but that several or more cases are presented at the Johns Hospital Dispensary which exhibit purely digestive complaints. The patients on careful examination are found to be suffering from——tuberculosis."

However, the gastro-intestinal symptoms which appear in the course of pulmonary tuberculosis are not always an expression of the pulmonary lesion. On the contrary, generally they are evidences of organic or functional disease of the digestive tract.

In a general way we observe that there are three groups of gastro-intestinal syndromes which occur in patients with pulmonary tuberculosis.

First, is the gastro-intestinal onset of pulmonary tuberculosis. These digestive symptoms are referred manifestations of the pulmonary disease. They are purely functional in character. Usually they clear up when the patient is given treatment for the pulmonary tuberculosis.

Second, are those incidental gastro-intestinal problems which occur in patients with pulmonary tuberculosis the same as in non-tuberculous persons. Elsewhere (4) we have discussed some of these incidental digestive problems. We have pointed out that patients with pulmonary tuberculosis can also have digestive disturbances resulting from protozoal infections, bacterial infections, tumors of the intestines,

functional disturbances of the colon, appendicitis, gastric disturbances, pancreatic disorders, nutritional disorders, blood dyscrasias, endocrine disorders, cardiorenal disease, etc.

Third, is intestinal tuberculosis which occurs in adults who have far advanced pulmonary tuberculosis. The common symptoms are diarrhea, abdominal pain, abdominal tenderness, abdominal rigidity, cramps after eating. The X-ray signs are spastic filling defects in the ascending colon, increased emptying time of the colon, dilatation and segmentation of the small bowel, ileal stasis and gastric retention. With some experience, intestinal tuberculosis is not a difficult diagnosis to arrive at.

It is the first group with which we are concerned in this paper, namely, those patients in whom the abdominal distress is an expression of the pulmonary disease.

The digestive onset of pulmonary tuberculosis is further illustrated by the following four case reports given in condensed form. In selecting the cases, we chose young persons who had been ill with tuberculosis a short time only, because they were close to the onset of their disease, and they would have keener memories of "their initiation into the brotherhood of the T.B.s." Patients with advanced tuberculosis were found to be unsatisfactory for this study, because they invariably became engrossed with their existing symptoms of cough, fever, loss of weight, chest pains, etc. and their memory of the onset became dulled.

Case 2. Gastro-Intestinal Onset of Pulmonary Tuberculosis.

I. T., a girl of 23 years, worked as a commercial artist. For the past year she had been distressed with diffuse abdominal pains in the umbilical and epigastric regions. This distress occurred whenever she overloaded her stomach. The distress was made worse by exercise. It was not related to the gastric cycle or to any particular type of food. At times she would experience a diffuse burning sensation in the epigastrium which would be made worse by milk or any food, but relieved by rest or external heat. At times the sensation spread and would involve the entire umbilical region. She had lost about ten pounds in the past few months; she tired easily, and had lost her pep. She did not cough, and had no night sweats, no appreciable sputum, no chest pains or any other respiratory symptoms, but felt warm at times.

Examination showed a young woman 5 feet 5 inches in height, weighing 110 pounds, not acutely ill.

There was an area of dullness to percussion in the right apex of the lung with bronchial breath sounds, increased voice fremitus and numerous rales. The X-ray showed a diffuse shadow in the right apex suggestive of pulmonary tuberculosis. Tubercle bacilli were found in the sputum.

The gastro-intestinal tract showed some ptosis, but otherwise it was within the normal limits.

Under rest treatment, the gastro-intestinal symptoms completely subsided, and the tuberculosis improved.

Case 3. Gastro-Intestinal Onset of Pulmonary Tuberculosis.

V. C., a boy of 12 years, complained of intermittent attacks of abdominal distress for several months. He would experience a disagreeable sensation in the upper abdomen manifested by a rumbling crampy distress associated with nausea, and sometimes followed by vomiting which would ease the distress. The attacks occurred when he was tired or ate a heavy meal. The attacks were not induced by any particular foods nor did they occur at any particular time of the day. He had not been gaining weight properly, and he tired easily. He had had the usual diseases of childhood and occasional winter colds; otherwise he had no



Fig. 1. X-ray film of patient F. R. Both apices and infraclavicular regions contain fibrotic and cavernous changes apparently due to a bilateral pulmonary tuberculosis. The hilum and bronchial markings are prominent. The heart is drop type and the thorax indicates the asthenic habitus. The diaphragm and costophrenic angles are normal.

complaints. He had no cough, no evident fever, no appreciable sputum. He never played very hard so did not know if he was short of breath.

Examination showed an undernourished boy weighing 57 pounds, 4 feet 5 inches in height.

There was impaired percussion over the left apex of the lung down to the fourth interspace. In this area the breath sounds were bronchial, and the whispered voice sounds were increased, also there were present some fine crackling rales. The X-ray film showed diffuse mottling in the left apical region of the lung. Tubercle bacilli were recovered from the gastric contents.

The gastro-intestinal tract was within normal limits.

Under sanatorium treatment, the digestive symptoms subsided.

Case 4. Gastro-Intestinal Onset of Pulmonary Tuberculosis.

P. K., a mail clerk of 25 years, complained of "stomach trouble" for six months in duration. He had been told that he had an ulcer of the stomach, but his symptoms did not improve under ulcer management. He complained of a burning sensation in the epigastrium when his stomach was full, which did not occur if he ate lightly; sometimes when his stomach was empty he had a different type of burning. Generally he was more comfortable if he ate lightly, and had distress if he overloaded his stomach. His abdominal distress was always made worse if he became excited or tired. He had lost about ten pounds in the past three months, he tired easily. Otherwise he had no complaint.

Examination showed an underweight young man not acutely ill but having a hectic flush on his face. He

weighed 120 pounds and was 5 feet 10 inches in height. The right apical region was dull to percussion, the breath sounds were bronchial, voice fremitus was increased, and numerous rales were heard. His temperature was 100.6, his pulse was 96, his respiration was 22, his blood pressure 104/54. The X-ray examination showed a shadow in the right apex. Tubercle bacilli were found in the sputum.

Under rest treatment, the digestive symptoms completely subsided.

Case 5. Gastro-Intestinal Onset of Pulmonary Tuberculosis.

F. R., a girl of 16, complained of abdominal distress, nausea and vomiting which was two months in duration. The distress was located in the epigastric and umbilical regions. It usually occurred when she became tired, then the distress appeared as a disagreeable burning sensation accompanied by nausea and sometimes followed by vomiting which relieved the distress. Otherwise she had no complaint. She did not cough, she had no appreciable sputum, no chest pains, she was not particularly short of breath, she had lost no weight and had no fever that she knew of, or night sweats. She had had the usual diseases of childhood and an occasional cold. A sister of hers had died of tuberculosis six months previously.

Examination showed a girl of 16 weighing 110 pounds, measuring 5 feet 2 inches in height. The tuberculin skin test was positive. There was dullness in both apical regions of the lungs accompanied by bronchial breathing, increased voice fremitus and rales. Tubercle bacilli were recovered from the gastric contents. X-ray showed diffuse mottling of the parenchyma of both lungs especially in the apices.

The digestive tract was within normal limits.

Under sanatorium treatment, the digestive symptoms subsided, although there was a spread of the tuberculous process of the lungs.

DISCUSSION

Tuberculosis is but one of many diseases which cause referred abdominal pain. Other causes mentioned recently in the literature of referred abdominal pain are: disturbances in the emotions, changes in the organic structure of the brain, alterations in the pelvis, changes in the renal system, in the anorectal region, in the cardiovascular system, etc.

In some of these diseases which give rise to referred abdominal pain there are certain convenient explanations to account for the mechanism of the referred digestive symptoms. Thus in gastro-intestinal symptoms of pelvic origin there are anatomic, neurologic, and chemical, relationships to explain the causation of the digestive symptoms. In abdominal symptoms of, cardiovascular origin, there are neurologic, and circulatory relationships. In gastro-intestinal distress of renal origin, there are anatomic, neurologic and chemical relationships. In gastric distress of brain origin, there are neurologic pathways to serve as mediums for the spread of impulses giving rise to the referred symptoms.

But in the digestive symptoms originating in pulmonary tuberculosis, there is present none of these convenient explanations. The explanation for the mechanism of the referred abdominal pain must be sought elsewhere. Since there are no evident direct relationships, indirect methods must be inquired into. A possible explanation may be found in the toxemia which occurs in tuberculosis.

This toxemia is composed of two factors. First, a specific toxemia elaborated by the tuberculous process, second, a non-specific toxemia elaborated by the fever process, independent of the tuberculosis.

That there exists a specific toxemia in tuberculosis has long been suspected clinically and is suggested by the work of Wildbolz (5) who in 1919 demonstrated that a tuberculin-like substance of specific antigenic nature which is excreted in the urine during the active stage of tuberculosis and which subsides when the disease becomes quiescent. Hanan and Zurett (6) believe that the biologic properties of the urinary tuberculosis antigen appears to be similar to O.T.

This specific antigenic substance is excreted through the kidneys from the blood stream. Being in the general circulation it is also carried to the other viscera of the body including the digestive tract where some of it is absorbed. It is even conceivable that the digestive tract may excrete some of it.

A similar situation exists in nephritis, where there occurs just such a chemical process. According to Elwyn (7), urea accumulates in the blood stream in pathologic quantities when the kidneys begin to fail in their function. Since urea diffuses easily, it soon makes its way into every organ in the body including the digestive tract. When urea in certain concentrations accumulates in the salivary glands it leads to a disagreeable taste, coated tongue and anorexia; urea in the glands of the intestines leads to diarrhea and other symptoms.

If urea in the digestive tract produces severe gastro-intestinal symptoms, it seems reasonable to suppose that a tuberculin-like antigen or "proteose" which may be present in large amounts during the active stage of the disease may likewise set up a digestive irritation.

In addition to the specific tuberculin-like antigen present in tuberculosis, there is present a non-specific toxemia, the by-product of the fever. According to Macleod (8), Best and Taylor (9) and others, certain chemical changes take place in the body metabolism during any fever of infectious origin. Among these changes are (1) an increased destruction of protein as indicated by an increase in the output of the creatinine, uric acid, purine bodies and albuminoses (proteoses) in the urine; also by the inability to maintain nitrogen balance in the patient without materially increasing the protein intake. (2) a definite tendency towards acidosis; (3) a disturbance in the salt balance of the body, salt retention occurs in the early stage of fever and is later removed by diuresis and diaphoresis; (4) a reduction in the urinary output in the early stage of fever.

Thus there appears to be an ample basis, both clinical and biochemical, for the presence of a toxemia, both specific and non-specific, in tuberculosis.

The referred gastro-intestinal symptoms which occur in tuberculosis as an expression of pulmonary disease can therefore result from the toxic effects of the disease on the digestive tract.

SUMMARY AND CONCLUSIONS

1. The onset of pulmonary tuberculosis is extremely variable.
2. It may suggest cardiovascular disease, menstrual disorders, neurasthenias or dyspepsias.
3. It may be entirely gastro-intestinal in character, and the patient may be treated for "stomach trouble" for some time before the true nature of the disease is uncovered.
4. The digestive onset is a referred abdominal

syndrome or a gastro-intestinal expression of the pulmonary disease.

5. However, not all the digestive symptoms which occur in pulmonary tuberculosis are referred syndromes. On the contrary, generally they are evidences of organic or functional disease of the digestive tract.

6. There are three groups of digestive symptoms which occur in patients with pulmonary tuberculosis. These are: (1) referred abdominal symptoms such as the digestive onset which is an expression of the pulmonary disease. (2) incidental digestive disturbances as peptic ulcer, gall bladder disease, etc., which occur in tuberculous persons the same as in the non-tuberculous; and (3) intestinal tuberculosis, a distinct complication of the pulmonary disease.

7. The referred abdominal symptoms are purely

functional in character and usually subside when the patient is treated for the pulmonary disease.

8. The mechanism of the production of the referred gastro-intestinal symptoms is considered as taking place through the toxemia which occurs in tuberculosis. The digestive symptoms are an expression of the toxic effects of the disease on the digestive tract.

9. The referred abdominal symptoms from pulmonary tuberculosis are not suggestive of the pulmonary lesion. If anything, they suggest a gastric irritation syndrome.

10. The diagnosis of pulmonary tuberculosis in these patients is arrived at by a careful physical examination aided by a roentgenogram of the chest, and such other laboratory tests which are essential to the proper analysis of the patient's ailment.

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The Control of Gastric Hyperacidity by Magnesium Trisilicate*

By

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FOR the control of gastric hyperacidity attention recently has been directed to the development and use of certain substances that absorb and inactivate the hydrochloric acid, rather than to those that act by direct chemical neutralization. Though little clinical experience with synthetic magnesium trisilicate has been reported, Mutch (1) states that it offers definite possibilities in this respect. Both Mutch (1) and Levin (3) have shown that, when titrated against dilute hydrochloric acid, it has an immediate anti-acid effect; also that for a prolonged secondary period it absorbs and inactivates the acid. In this report I shall compare, in a series of hyperacidity cases, the action of magnesium trisilicate with that of a similar dosage of a mixture of sodium bicarbonate, 2 parts, calcium carbonate, 2 parts, and the heavy oxide of magnesium, 1 part.

Thirty-six subjects, all ambulatory duodenal ulcer cases, were used for the investigation. In 24 of this group the effect of magnesium trisilicate was studied under fasting conditions. In the remaining 12, the effect of the drug was studied in association with frequent feedings.

I. EFFECTS UNDER FASTING CONDITIONS

Procedure: In 24 fasting subjects the total gastric content was extracted through a small tube, and its

free hydrochloric and total acid values determined. Magnesium trisilicate, 2 gms. in 25 cc. of distilled water, was then given by mouth and small samples of gastric juice aspirated every fifteen minutes for a period of four hours. The fractions thus secured were titrated immediately with N 50 sodium hydroxide, using Töpfer's reagent and phenolphthalein as indicators. The samples taken after the administration of magnesium trisilicate were titrated at once since even a small amount of the drug will continue to lower the acidity after aspiration.

This procedure was subsequently repeated with the alkaline mixture (2 gms. of sodium bicarbonate, calcium carbonate and heavy magnesium oxide) instead of magnesium trisilicate.

Results: The free hydrochloric acid of the stomach contents in this group, while fasting, ranged from 24 to 74, and the total acidity from 44 to 108 units (Fig. 1). Following the administration of the magnesium trisilicate a moderate reduction in the gastric acidity was observed within fifteen minutes; the maximal reduction was reached after thirty minutes, and it was maintained for approximately one hour. A gradual rise in the acid curve followed, reaching the original value within three hours.

Administration of the alkaline mixture (Fig. 2), on the other hand, resulted in a rapid reduction in gastric acidity which was maximal within fifteen minutes. The reduction was less well maintained than that following the magnesium trisilicate. The curve began

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to rise immediately and reached its original level within one and a half hours.

II. EFFECTS OF ALTERNATE ADMINISTRATION OF MAGNESIUM TRISILICATE AND FOOD

Since the magnesium trisilicate gave a more prolonged period of reduced gastric acidity, an attempt was made to determine whether or not alternate administration of this drug and interval feedings would maintain the acidity at, or near, the lowered level throughout the entire day.

Procedure: Twelve subjects with uncomplicated duodenal ulcer were employed. The fasting gastric con-

tent was removed in the usual way at 9 A. M. and its free and total acid values determined. Hourly fractions were withdrawn for analysis throughout the entire test period, which ended at 5 P. M. Immediately following the aspiration of the fasting gastric content, a meal consisting of one soft boiled egg, two slices of buttered toast and 240 cc. of equal parts of milk and cream was given. This meal was repeated four hours later (1 P. M.). Two grams of magnesium trisilicate were given one hour after each of these feedings and an interval feeding, consisting of 240 cc. of equal parts of milk and cream, was given midway between the meals and two hours after the second one. This regimen was intended to simulate as closely as

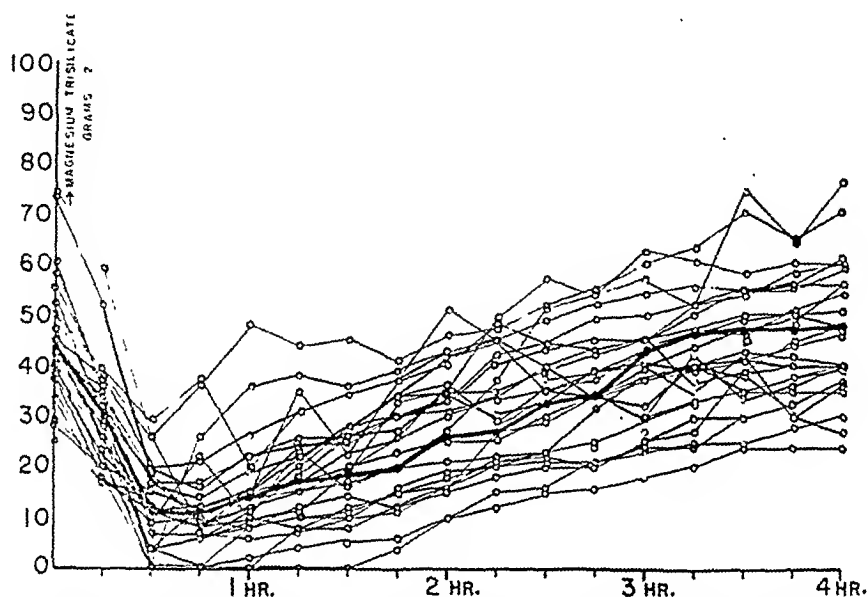


Fig. 1. Curves showing the effect of the administration of 2 gms. of magnesium trisilicate on the free hydrochloric acid of the stomach contents in 24 subjects. The heavy line represents the average of all the curves.

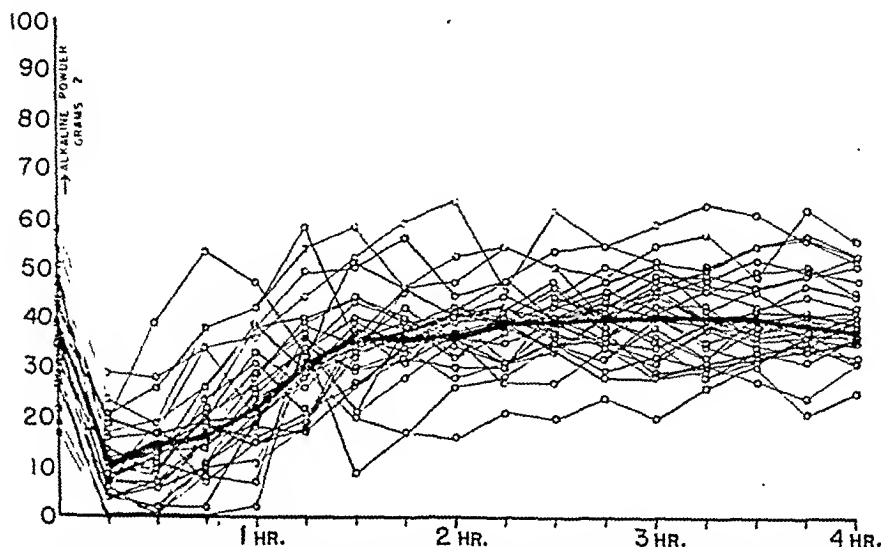


Fig. 2. Curves showing the effect of the administration of 2 gms. of alkaline mixture on the free hydrochloric acid of the stomach contents in 24 subjects. The heavy line represents the average of all the curves.

possible the usual feeding routine of our ambulatory ulcer patients.

On a subsequent day the same patients followed a similar program, except that 2 grams of the alkaline mixture replaced the magnesium trisilicate.

Results: Neither the magnesium trisilicate nor the alkaline mixture with the feedings gave a persistent achlorhydria (Figs. 3 and 4). In all instances, following the ingestion of the meal a substantial reduction in the free gastric acidity occurred. Following the administration of magnesium trisilicate there was a second, less marked, reduction in acidity which, with the aid of the interval feeding, was maintained for

approximately two hours. At the end of this period a definite rise in acidity occurred. When the alkaline mixture was employed one hour after the regular meals, a secondary drop in acidity was not consistently observed. If a reduction in acidity occurred at this point it was not maintained until the next fraction was aspirated one hour later.

By comparing Figs. 3 and 4 it will be noted that the free acid, except for a noon-day rise, was kept below its original value throughout the entire test period when magnesium trisilicate was used. The curve produced when the alkaline mixture was employed was generally higher and more irregular than that with

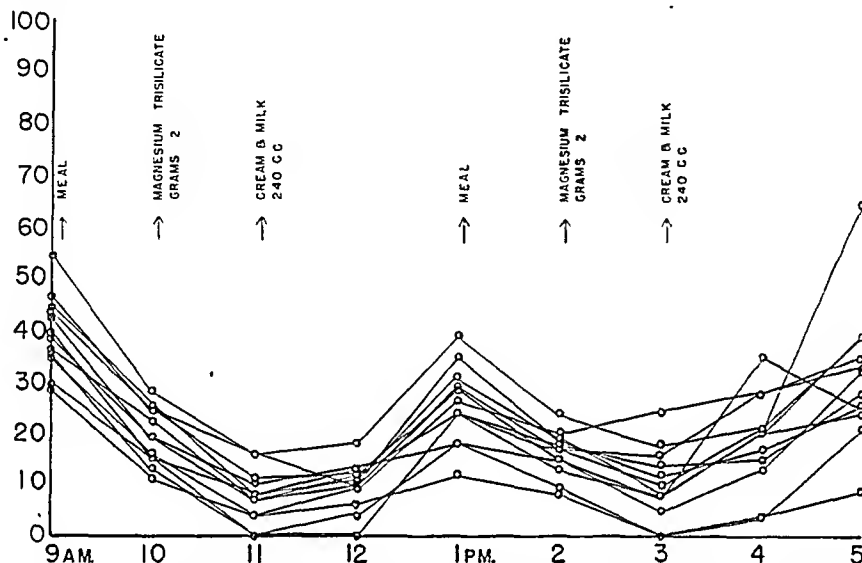


Fig. 3. Curves showing the effect of the administration of magnesium trisilicate and interval feedings on the free hydrochloric acid of the stomach contents in 12 patients over an eight-hour period.

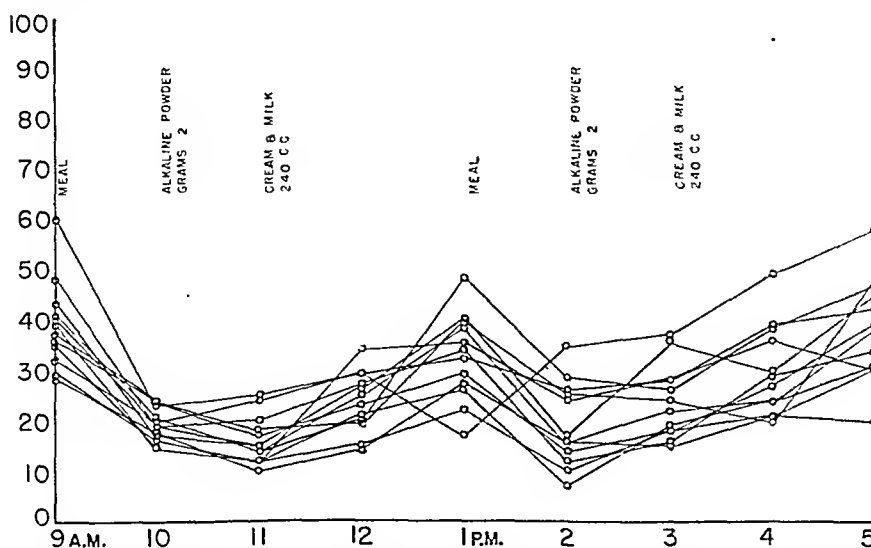


Fig. 4. Curves showing the effect of the administration of the alkaline mixture and interval feedings on the free hydrochloric acid of the stomach contents in 12 patients over an eight-hour period.

magnesium trisilicate. The chief difference, therefore, between the two curves was one of degree in reduction.

DISCUSSION

The use of magnesium trisilicate seems to offer some advantages over the ordinary alkaline mixture in the control of gastric hyperacidity. A single dose gives a longer period of reduction in gastric acidity, although the alkaline powder is more rapid in its action. Any drug which will prolong the period in which gastric acidity is reduced offers a very real advantage to ulcer patients. This is particularly true in those who for any reason do not have access to frequent medication and interval feedings. For example: A longshoreman, whom we observed, could not, because of the nature of his work, secure interval feedings. Alkaline powders gave him only temporary relief from his discomfort. Magnesium trisilicate, however, afforded relief for from two to three hours, and entirely solved the problem of keeping him symptom-free. It is not uncommon for peptic ulcer patients to be awakened at night because of epigastric discomfort. Frequently the use of magnesium trisilicate taken just before retiring will give complete relief from this night distress. In other patients it may be necessary to take the drug an hour before those periods when the pain usually occurs.

Magnesium trisilicate is innocuous in large doses, producing no gastro-intestinal symptoms even after prolonged use. Hydrated silica, which is produced on contact with the gastric acid, is an inert substance. Mutch (2) gave rats large doses of magnesium trisilicate over a period of six months and their descendants, through the third generation, were given similar doses. No abnormality in appetite, growth or elimination was noted. Postmortem examination failed to reveal any significant abnormalities. Of our 36 cases, not one complained of any gastro-intestinal disturbance during the magnesium trisilicate administration. It produced neither constipation nor diarrhea, while alkaline mixtures, particularly those containing magnesium, frequently produce diarrhea, and the use of aluminum hydroxide is not infrequently complicated by obstinate constipation. Furthermore, magnesium trisilicate in combination with the gastric acid does not produce gas and the resultant sensation of epigastric distention which so frequently follows the use of alkaline mixtures. Not being absorbable it cannot

produce an alkalosis, which so frequently results from the continued use of alkalis and which constitutes the chief practical objection to their routine use.

Magnesium trisilicate is a powerful absorbent. At the saturation point with methylene blue it is seven-teen times as active as colloidal kaolin (Mutch (1)). It has been shown that it will protect experimental animals against lethal doses of various toxins and poisons, as that produced by the shellfish. (Mutch (2)). Both magnesium trisilicate and hydrated silica gel absorb pepsin from the upper gastro-intestinal tract. The pepsin thus absorbed, however, is not destroyed, but is still available for the digestion of protein food material (Mutch (2)). Since it is such a powerful absorbent in the gastro-intestinal tract magnesium trisilicate may be a valuable addition to our armamentarium against acute food poisoning. Before it is accepted without reservation, however, further study is needed as to its effect on other constituents of the gastric secretion and on the absorption of food, vitamins and minerals from the intestine.

Finally, in view of the rise in the acid curves (Figs. 3 and 4) after the intermediate feedings, it is suggested that better results could be obtained by giving the magnesium trisilicate, as is customary with alkaline powders, between every two feedings.

CONCLUSIONS

1. Magnesium trisilicate is a satisfactory substitute for the alkalis commonly employed to control gastric hyperacidity; in the same dosage it is slightly less prompt in its neutralizing action, but its effect is somewhat more prolonged.

2. Its chief advantages over the alkalis consist in its more prolonged neutralizing action, its absence of effect on the bowels and its non-absorbability, the latter precluding the possibility of a resultant alkalosis.

The magnesium trisilicate used in this study was supplied by Eli Lilly & Co. under the trade name of "Trisomin."

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Studies in Human Biliary Physiology*

II. The Effect of Food Factors and Orally Administered Bile On the Rate and Quantity of Bile Secretion

By

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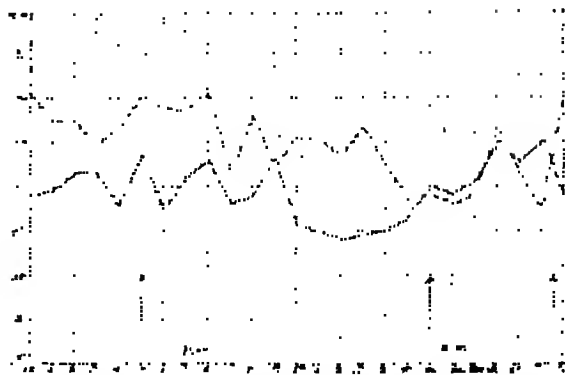
IN a previous paper (1), we reported our findings on the rate and quantity of bile secreted hourly by a cholecystectomized human with a normal liver and

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a total external biliary fistula. These observations were made on the fasting subject to whom none of the bile collected from the fistula was re-fed orally, and represented basic values for bile secretion by the liver. The great diversity of opinion expressed in the litera-

ture concerning the effect of various food factors on bile secretion prompted us to investigate the changes in these basic values produced by the feeding of varied diets, alone and in conjunction with orally administered bile.

For the sake of brevity, the opinions of only a few investigators will be mentioned. Thus, in regard to the effect of protein on bile secretion, Nasse and Ritter (2), Bidder and Schmidt (3), Foster, Hooper and Whipple (4), Wolf (5), Specht (6), Winogradow (7), Stransky (8), Brunacci and Noferi (9), among others, have reported increases in bile secretion with protein diets. Moreover, Barbera (10), and Kocour and Ivy (11) have observed the greatest food-produced cholerisis to result from a meat diet. On the other hand, Okada (12), Koster, Shapiro and Lerner (13), Josephson and Larsson (14), and Kohlstaedt and Helmer (15) report no particular increase in bile secretion as a result of a meat diet. With respect to fats, Nasse and Ritter (2), Rosenberg (16), Barbera (10), Fleig (17), Brunacci and Noferi (9) Iwanaga (25), Weinberg (18), and Rost (19), have reported choleretic effects with fat diets, whereas Bidder and Schmidt (3) were of the opinion that fats have a depressing effect on bile secretion. Prevost and Binet (20), Doyon and Dufourt (21), Voit (22), and Kocour and Ivy

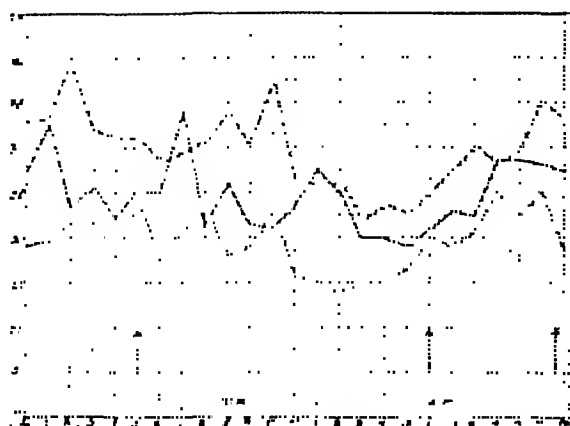


Graph 1. Hourly secretion of bile in the fasting state (solid line) and after administration of 300 cc. of bile orally (broken line), 100 cc. at each feeding. Arrows indicate time of bile administration. Note post-cibum cholerisis.

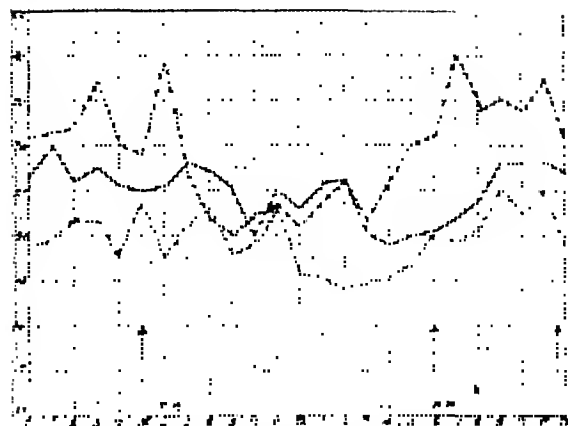
(11) have expressed the belief that fats have no effect, one way or the other, on bile secretion. In the case of the carbohydrates, Nasse and Ritter (2) have noted a small increase in bile secretion with carbohydrate diets, while Barbera (24), Kocour and Ivy (11) and Brunacci and Noferi (9) have noted no effect, and

TABLE I
Hourly secretion of bile on type diets with and without the addition of orally administered bile

Time	No Food 300 cc. Bile (100 cc. t.i.d.)	Mixed Diet		High Fat Diet		Pure Carbohydrate Diet		High Protein Diet	
		Alone	Plus Bile 300 cc.	Alone	Plus Bile 300 cc.	Alone	Plus Bile 300 cc.	Alone	Plus Bile 300 cc.
P. M. 12-1	27.5	32.4	33.0	30.0	31.5	19.1	25.0	32.0	36.1
1-2	27.4	23.3	35.0	26.5	32.0	19.6	27.4	32.4	31.0
2-3	25.3	25.7	32.0	27.5	37.0	20.1	26.0	29.0	35.7
3-4	26.4	22.2	31.0	25.8	30.0	19.5	26.5	32.0	35.2
4-5	30.8	25.1	31.0	25.3	29.0	20.0	30.0	30.1	35.5
5-6	29.2	25.0	28.5	25.5	39.0	20.4	29.5	28.4	30.9
6-7	28.5	34.0	33.3	28.0	27.0	22.5	30.2	29.6	30.2
7-8	30.7	21.3	30.5	27.0	22.2	22.6	30.5	28.9	31.1
8-9	21.7	26.1	33.8	25.0	20.0	21.8	26.0	29.0	37.5
9-10	27.9	21.4	30.0	20.0	22.1	22.0	27.0	23.0	25.4
10-11	22.4	21.0	37.0	25.0	23.5	21.1	24.5	23.2	27.6
11-12	25.3	23.7	26.0	23.0	21.0	20.9	25.1	21.8	26.2
A. M. 12-1	25.5	27.4	26.0	23.5	23.5	21.0	26.0	19.0	20.2
1-2	23.5	25.1	26.0	26.0	25.8	20.5	25.8	20.8	20.4
2-3	27.0	20.0	22.0	20.0	21.4	21.6	25.4	22.6	22.1
3-4	22.6	20.0	23.5	19.0	25.8	20.8	23.0	20.6	19.5
4-5	18.7	19.0	22.5	20.0	30.0	22.0	20.0	19.7	21.5
5-6	19.0	20.8	25.0	20.5	31.2	19.8	21.1	24.8	25.8
6-7	18.0	23.0	27.4	22.1	40.0	20.1	20.0	30.7	30.4
7-8	18.9	22.7	30.0	23.9	32.0	21.0	21.6	33.8	32.5
8-9	26.4	28.6	28.0	28.0	35.0	22.0	23.0	36.5	37.5
9-10	21.6	28.6	29.0	28.2	34.2	23.8	22.4	35.5	40.3
10-11	17.8	28.4	35.2	28.0	37.5	21.0	20.4	38.2	41.2
11-12	30.5	27.6	33.0	27.0	31.0	18.8	30.0	34.0	38.4
Total	592.6	592.4	712.7	596.8	703.0	499.0	610.3	688.6	742.4



Graph 2. Hourly secretion of bile after administration of mixed hospital diet alone (solid line) and with the addition of bile at each feeding (broken line). Arrows indicate time of feeding. Compare with bile secretion in the fasting state (dotted line) and note choleresis induced by diet and the additive rise induced by feeding bile with the diet.



Graph 3. Hourly secretion of bile after administration of a high fat diet alone (solid line) and with the addition of bile at each feeding (broken line). Dotted lines indicate bile secretion in the fasting state. The choleric effects noted are of the same order as those induced by a mixed diet (compare with Graph 2). Arrows indicate time of feeding.

Afanassiev (23), Weinberg (18), and Foster, Hooper and Whipple (4), an actual depression.

Procedure: For these studies, the subject was first allowed a standard mixed hospital diet for several days, following which she was starved for 24 hours to establish basic fasting conditions. When this state was reached, she was put on the test diet for a period of three days before bile samples were taken. On the fourth day of the test diet, the bile was collected hourly from the leak-proof fistula, for 24 hours. Throughout this investigation, the subject remained at rest in bed, and her daily water intake was kept constant. Before each new test diet was employed, the subject was fed a routine mixed hospital diet for several days followed by a 24 hour fasting period to bring her bile secretion values to a basic fasting state. The following test diets were employed being repeated on four occasions for each diet:

1. No food, but 300 cc. of subject's own bile, collected from fistula tract, fed orally, 100 cc. at each of three feedings.

2. Routine mixed hospital diet (P-75 C-200 F-100)

with no bile by mouth. Caloric value of diet 2027 calories.

3. Routine mixed diet plus 300 cc. of bile, 100 cc. with each meal.

4. High fat diet (P-75 C-90 F-212), no bile by mouth. Caloric value of diet 2584 calories.

5. High fat diet plus 300 cc. of bile, 100 cc. with each meal.

6. Pure carbohydrate diet (C-400), no bile by mouth. Caloric value of diet 1640 calories.

7. Pure carbohydrate diet plus 300 cc. of bile, 100 cc. with each meal.

8. High protein diet (P-200 C-90 F-100), no bile by mouth. Caloric value of diet 2089 calories.

9. High protein diet plus 300 cc. of bile, 100 cc. with each meal.

Table I represents an outline of the characteristic type values of the rate and distribution of bile secretion under the above-mentioned dietary regimens.

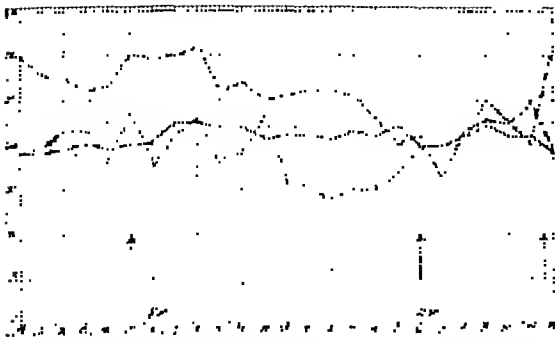
ANALYSIS AND DISCUSSION

An analysis of the observed values charted in Table I and summarized in Table II appears to indicate that

TABLE II
Summary and evaluation of data charted in Table I

Diet Type	1. Fasting Value (basic)* cc.	2. Food Alone cc.	3. Increase by Food Alone (col. 2 minus col. 1) cc.	4. Food and Bile cc.	5. Bile and No Food cc.	6. Increase by Bile and Food Over Fasting (col. 4 minus col. 1) cc.	7. Increase by Bile and Food Over Food Alone (col. 4 minus col. 2) cc.
300 cc. bile and no food	182.0	—	—	—	592.6	—	110.6 (col. 5 minus col. 1)
Mixed diet (normal)	182.0	592.4	110.4	712.7	—	230.7	120.3
High fat	182.0	596.8	114.8	703.0	—	221.0	106.2
Pure carbohydrate	182.0	499.0	17.0	610.3	—	128.3	111.3
High protein	182.0	688.6	206.6	742.4	—	260.4	53.8

*Fasting value determined by Zerkow, Kozut and Jacobl. To be published, Ref. 11.



Graph 4. Hourly secretion of bile after administration of a pure carbohydrate diet alone (solid line) and together with bile at each feeding (broken line). Arrows indicate time of feeding, dotted line the bile secretion in the fasting state. Note absence of choleretic attributable to carbohydrate feeding (compare with Graph 1).

the feeding of a carbohydrate diet produced a negligible increase of bile secretion over basic starvation values, the figures being respectively 499.0 cc. and 482.0 cc. in 24 hours. A high fat diet produced no increase over an average mixed diet containing one-half the quantity of fat and in which the protein factor remained constant, the increases over fasting values being respectively 114.8 cc. and 110.4 cc. in 24 hours. The greatest increase in bile secretion occurred when the subject was fed a high protein diet, the increase over the fasting value being 206.6 cc. in 24 hours. On an average mixed diet, the increase in bile secretion was variable, depending apparently on the amount of protein included in the diet, and to a negligible degree on the fats and carbohydrates. The mixed diet employed, containing a little less than half the amount of protein contained in the high protein diet, produced a choleretic effect approximately one-half that produced by a high protein diet. The apparent increase in quantity of bile secreted on a high fat diet being of the same order as that produced by a mixed diet with similar protein content suggests that the rise obtained is a resultant of the protein in the diets administered.

The caloric content of the diets used apparently plays no part in the choleretic effects observed. Thus the high fat diet, with a 27% increase in calories over that of the mixed diet, induced an increase in the quantity of bile secreted equal to that induced by the mixed diet. On the other hand the high protein diet, with only a 3% increase in calories over that of the mixed diet, induced a choleretic effect twice as great. Similarly a 19% decrease in total calories in the carbohydrate diet as compared with the caloric value of the mixed diet could not be related to the absence of any rise in quantity of bile secreted.

Orally administered bile alone had a choleretic effect equal to that of the ordinary mixed diet, namely 110.6 cc. more than the fasting value. The addition of bile to the various types of diet produced a considerable increase in the quantity of bile secreted with all the test diets, the increase over the fasting values being 230.7 cc. with a mixed diet, 221.0 cc. with the high fat diet, 128.3 cc. with a pure carbohydrate diet, and 260.4 cc. with the high protein diet. Moreover, the choleretic effect of orally administered bile and type diet seemed

to be additive, approximating the sum of the increases produced by either bile or type diet when used alone. The exception to this, however, occurred with a high protein diet, where the increase by food alone over the fasting quantity, namely 206.6 cc. was so great as to make the additional rise produced by the added bile equal to only one-half the value obtained when bile alone was fed to the fasting subject, namely 53.8 cc. as compared to 110.6 cc. This would seem to indicate that a maximum secretion of bile can be obtained by various stimuli but that additional stimulation will not produce added secretion beyond this maximum.

Examination of the graphs illustrating the distribution of bile secretion during the day under these varying conditions revealed no important consistencies (see graphs 1-5). The greatest hourly flows occurred in from one to three hours after the ingestion of the test diet. Various secondary rises in rate of secretion, lower, however, than the post-cibum rises, were noted at varying periods during the day and night. These secondary rises showed no uniformity either in time or quantity.

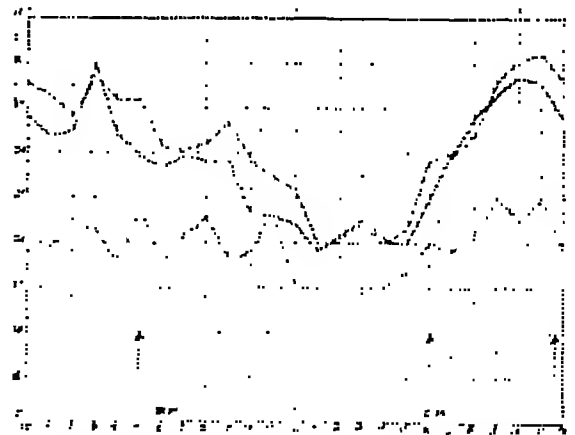
SUMMARY AND CONCLUSIONS

1. A high protein diet administered to a cholecystectomized subject with a total external biliary fistula produced consistently the greatest increase in quantity of bile secreted. This increase was approximately twice as great as that produced by either a high fat diet or an average mixed hospital diet. The increased secretion produced by the latter two diets was of the same order. Pure carbohydrate diets produced no increase in quantity of bile secreted over that secreted under basic fasting conditions.

2. It is suggested that fat alone has no choleretic effect.

3. The oral administration of bile alone produced a rise in biliary secretion of an order comparable to that produced by a mixed hospital diet.

4. The addition of bile to the high fat, mixed, or



Graph 5. Hourly secretion of bile after administration of high protein diet alone (solid line) and together with bile at each feeding (broken line). Arrows indicate time of feeding, dotted line the bile secretion in the fasting state. Note the consistently increased choleretic compared with that induced by a mixed and high fat diet (see Graphs 2 and 3). Note the virtual absence of additive effects upon bile feeding. The post-cibum rises are sharper than with the other diets.

pure carbohydrate diets used, produced an additive effect on bile secreted by the patient. This effect was not noted with the use of high protein diets.

5. It is suggested that there exists a maximum response of the liver to bile secretory stimuli.

6. Maximal secretory increases occurred from one to three hours following the administration of the test

diets and bile. Various irregular and unexplained slight secondary rises were noted not in relation to the ingestion of food or bile.

7. Caloric content of the diets used does not influence cholerisis.

8. In these experiments no food factor evoked a depressing effect on cholerisis.

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Treatment

VOMITING

In an article on acute upper respiratory infections with gastro-intestinal symptoms published in Minnesota Medicine for September, 1938, page 611, E. D. Anderson stated that when children are vomiting excessively the most useful drug he has found is chloral hydrate given by rectum. It also relieves the abdominal pain.

A HINT IN GIVING SULFANILAMIDE

In the Journal of Clinical Investigation, November, 1938, page 699, Hartmann, Perley and Barnett commented on the fact that when given in large doses, sulfanilamide commonly produces methemoglobin and the patient has a dusky hue. This occurs in most cases when 0.1 gm. or more is given per kilo. per twenty-four hours. The cyanosis can be combated by giving intravenously a single dose of from 1.0 to 2.0 mg. per kilo. of methylene blue. This can be given also orally in doses from 1.0 to 2.0 grains (65 to 130 mg.) every four hours. It can be given at the same time as the sulfanilamide is given.

THE TREATMENT OF ACUTE ALCOHOLISM

In Cobb's review of neuropsychiatry for 1938, published in the Archives of Internal Medicine for November, he quotes Nicholson and Taylor (Jour. Clin. Investigation, 17:279, 1938) who stated that many of the symptoms of an alcoholic hangover are probably due to dehydration. Thomas, Semrad and Schwab (Am. J. Med. Sci., 195:820, 1938) showed

that patients with delirium tremens improved more rapidly if given much water intravenously and by mouth. Paraldehyde is the best sedative. The impression now is that there is no need for withdrawing alcohol slowly.

THE TREATMENT OF ACUTE CEREBRAL THROMBOSIS

Not infrequently the gastro-enterologist is called to see an elderly person who is supposed to have acute indigestion because he or she has suddenly started to vomit. Actually, a little study will show that the patient has had a stroke. In an interesting review of neuropsychiatry by Stanley Cobb, in Archives of Internal Medicine, November, 1938, the statement is made on page 888 that the best cerebral vasodilators are carbon dioxide, glyceryl trinitrate, acetylcholine, ether, and alcohol. Cobb believes that they should be used early in cases of cerebral thrombosis because if the circulation can be restored to an infarcted area within a few hours of the onset, a good deal of function can probably be saved which might otherwise be lost if the usual treatment with morphine were followed.

Waldbott and Ascher (J. Allergy, 9:584, 1938) found positive skin reactions in only 27 per cent of 116 cases of urticaria. Rackemann (Arch. Int. Med., 63:173, 1939) states that his experience agrees closely with that.

Editorials

CORONARY THROMBOSIS

UNLESS the gastro-enterologist is constantly on the watch for cases of coronary narrowing or actual thrombosis, he is very likely to miss them and to be surprised when some flatulent old man seen by him drops dead. Unfortunately, in many cases of this

type, especially when no infarct has as yet been formed, the electrocardiogram does not help in making the diagnosis. The diagnosis can often be made, however, if the patient gives a story of being unable to walk any distance after dinner. After going a few blocks the man will develop a pain or distress in the

chest which will cause him to stop for a few minutes. Then he can go on again. In between times, such patients will often have attacks of flatulence, and then perhaps the only reason why the gastro-enterologist will think of the right diagnosis is that the patient is a man past forty who never had flatulence before he became somewhat short of breath on hills. Sometimes the flatulence will come after the patient has played too strenuously at golf or has lost his temper or has dug in his garden or has walked against a cold wind.

The paper by Gorham and Martin in the *Archives of Internal Medicine*, November, 1938, page 82, is a bit discouraging to would-be diagnosticians because on studying 100 patients with proved coronary occlusion they found that 42 never had any cardiac pain. This shows how difficult the diagnosis may be and why the gastro-enterologist must often fail to give a correct opinion in these cases. Often he can hardly be blamed for making a mistake. Fortunately for the diagnostician, in the group of Gorham and Martin's patients who did not have pain, dyspnea was generally present and well marked. In many cases old infarcts were present in the heart and their presence might have been revealed by an electrocardiogram. Recent infarcts can sometimes be suspected when the patient has a high blood sedimentary rate. This is probably due to the absorption of necrotic tissue in the heart.

Walter C. Alvarez, Rochester, Minn.

THE INCIDENCE OF DUODENAL ULCER AMONG AMERICANS

THE question often arises: What is the incidence of duodenal ulcer in the population of the country as a whole? Naturally one cannot take the incidence of ulcer in various hospitals or clinics because persons with ulcer will go to a clinic more often than will persons who haven't ulcer. All medical statisticians will be interested, then, in the report of Dr. Jennison in the November, 1938, number of the *American Journal of Medical Sciences*, page 654. There one finds a study of the cases of ulcer turned up among 14,000 persons working in the home office of the Metropolitan Life Insurance Company during the years between 1927 and 1936. Most of these persons were employed in executive or clerical work. Their ages ranged between eighteen and seventy years. As one would expect, most of the employees were between twenty and twenty-nine years of age. The ratio of women to men was roughly 2.5 to 1.

Twenty-seven hundred of the employees were examined with the fluoroscope and in this group a diagnosis of duodenal ulcer was made in 191, or 7 per cent. Dr. Jennison had the impression that these 191 cases probably represented practically the entire incidence of duodenal ulcer in the 14,000 persons. This gives an incidence in the whole group of 1.38 per cent. There probably were some persons, however, who had ulcers which were not producing enough symptoms to cause them to consult the company physician.

It was interesting to note that some of the patients with ulcer had recurrences almost every year, while others had longer remissions. Hemorrhage occurred in 10.5 per cent of the cases: in 14 men and 6 women. Eleven patients were treated surgically: 8 men and 3 women. The usual operation was a posterior gastro-enterostomy. Three of these patients have already

had to have secondary operations. In one of them the first operation was a simple suture of a perforating pyloric ulcer. One of the others had to have a gastric resection for jejunal ulcer, and the other patient, a woman, had to have a partial gastrectomy for repeated hemorrhages. Since the gastrectomy she has had another hemorrhage requiring transfusion. Curiously, one of the patients with duodenal ulcer died of a gastric carcinoma.

Of the 191 patients, 139 have lost no time from work because of their ulcer symptoms; the other 52 patients have lost, because of their disease, a total of 4,156 days during the ten-year period. This really isn't very much considering the fact that half of the time lost was due to hemorrhages which temporarily prostrated twenty of the 191 patients.

Walter C. Alvarez, Rochester, Minn.

THE NEED FOR THE PHYSICIAN'S GRIPPING THE PATIENT TO HIM

PHYSICIANS will do well always to read every article that ever comes from the pen of Dr. John H. Stokes. Always they will find an ideal presentation of the subject, and always they will find vivid speech, delightful humor, much food for thought, and for the development of a philosophy in medicine.

We just happened to pick up a paper by Stokes on "Clinical problems in syphilis control today" published in the *Journal of the A. M. A.* for March 6, 1937, and there we find as usual several vivid statements that made us think. Speaking of some of the difficulties of getting physicians to change over from the old to the modern conceptions of the treatment of syphilis, Stokes wrote, "Little short of a public education backfire will remove this standing block of dead professional timber from the path of progress. The call, therefore, is for torches." There is much need for such backfire also in the field of cancer recognition and treatment.

In his conclusion he wrote, "While the door closes may I remark that all that has gone before is reduced to nothing unless you bring your patient to an unswerving allegiance to yourself and all you represent and advocate, by such a humanity of approach, such an anticipation of his needs and problems as a being like yourself, as only the heart can compass. Injections of chemotherapeutic agents are merely mediated by the hand and head. Effective treatment for syphilis may indeed be mechanized to a certain perfection by knowledge. But the uprooting of the disease from its hold on humanity is done by the eye, the voice, the understanding and sympathetic spirit, without which all our much gathering of knowledge is but the unliving dust." If this holds true, as doubtless it does, for the treatment of a definite organic disease like syphilis, which is to be treated with drugs that search out and kill the spirochetes, how many hundred times more true must it be of the functional forms of indigestion in which no organic disease can be found and in which no cure can be accomplished unless the patient can be made to see the true nature of his trouble and be induced to make a strong effort to mend his or her ways.

Walter C. Alvarez, Rochester, Minn.

THE LOCATION IN THE BRAIN OF THE LESIONS WHICH ARE MOST COMMONLY ASSOCIATED WITH PEPTIC ULCER

FOR some time it has been known that certain lesions of the brain are commonly associated with peptic ulcer, but it hasn't been known just what type of intracranial lesion is most likely to produce such ulcers, and almost nothing is known of the way in which the gastro-duodenal mucosa is weakened and injured. We are glad to note, therefore, a report by Oppen and Zimmerman (Yale Journal of Biology and Medicine, October, 1938) of a study of 21 cases of intracranial lesions in which there was an associated injury to the mucosa of the upper part of the digestive tract. In 16 instances the lesion was in the nuclei of the interbrain. There were 2 in which it was in the midbrain and another 2 in which there was a diffuse, mainly cortical lesion.

The injury to the digestive tract was thought to be effected through the hypothalamic nuclei. There were 2 cases, however, in which injury to the diencephalon and mesencephalon was not associated with lesions of the digestive tract. More studies along this line are needed, and it may well be that they will throw valuable light on the mechanism of ulcer production.

Koga (Arch. f. klin. Chir., 188:449, 1937) reported experiments on rabbits in which the brain was injured in the region of the third ventricle. In a third of the animals there were hemorrhages and erosions of the gastric mucosa. Chiariello (Rassegna internaz di clin. e terap., 18:489, 1937) produced lesions involving the optic thalami in dogs and found hemorrhagic changes in the mucous membrane of the stomach. He gained the impression that the optic thalami constitute a trophic center for the digestive mucous membrane. Martin and Schnedorf (Am. J. Physiol., 122:81, 1938) working with monkeys and cats, electrocoagulated

small areas of the hypothalamic area, but found no changes in the stomach. Vanzant and Brown (Am. J. Dig. Dis., 5:113, 1938) reported the appearance of peptic ulcer in a child shortly after an injury to the brain.

Walter C. Alvarez, Rochester, Minn.

SIMMOND'S DISEASE AND ANOREXIA NERVOSA

DURING the last year or two there have been a number of reports in the literature which show a decided turning away from the idea that Simmond's disease is fairly common. The more carefully clinicians study patients with what might at first glance seem to be Simmond's disease and the more intelligently they handle these patients, the more often they come to the conclusion that the trouble was really anorexia nervosa. There is a good discussion of the subject in the January, 1939, issue of *Archives of Internal Medicine* by Henry B. Richardson. There was another discussion briefly reported on in the March 11 issue of the *Journal of the A. M. A.*, page 1007. At a meeting of the Royal Society of Medicine, Dr. Ryle reported 63 cases of extreme emaciation, most of them in girls and unmarried women under thirty years of age. The majority of these women were psychoneurotic and some were psychopathic. What started most of them off was either an emotional disturbance, overwork, or efforts to reduce weight because of ridicule by friends. Once started on the way to emaciation these neurotic women seemed to enjoy the interest which was excited by their illness. The several discussants of Ryle's paper agreed with him that the present day tendency to diagnose Simmond's disease in cases of this type is unfortunate.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

Syphilis. Presented by the Section on the Medical Sciences. Edited by Forest Ray Moulton. Published by The Science Press, 1938.

THIS attractive book of 193 pages is the third of a series of reports of symposia on important problems of public health, presented before the section on medical sciences of the American Association for the Advancement of Science. Each one of these symposia has been planned carefully with the help of experts, and leading specialists have been invited to discuss the several topics into which the subject was divided. The papers were later edited and published in one volume.

The list of contributors to this volume contains the names of the leading syphilologists of the country. An effort was made to bring out what is known about the origin of syphilis and its relation to yaws and a disease known as bejel. In speaking about bejel, Dr. Hudson stated that nine in ten of the Arabs of the middle Euphrates have syphilis, which is acquired usually in infancy or childhood. Curiously, among these people this type of syphilis does not interfere

much with the virility of the men or the fertility of the women. The disease is peculiar also in that it tends more to mutilate the nose and throat, and to attack the skin. It is suggested that this type of syphilis was widespread in antiquity, and since it was acquired in childhood no one ever had reason to think of it as a venereal disease. It may have become a venereal disease when it attacked the people of Western Europe in the fifteenth century. Interestingly, bejel resembles yaws in many respects. And, speaking of yaws, one finds in one chapter Dr. Butler's argument that syphilis and yaws are one disease, and in the next chapter Dr. Fox's argument that they are different diseases.

This little book is particularly valuable in that every effort has been made to present what is known of the biology of the *Spirocheta pallida* and of its reactions to drugs and to the defensive powers of the body. Every physician, no matter in what field he practices, can profit by reading this book; he can go through it as he would through a story book, with great interest and pleasure.

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Treatment in General Practice. 2 volumes, Boston, Little, Brown and Company, 1939. Price \$7.50.

A few years ago the British Medical Journal tried an experiment. It published a long series of articles on the treatment of disease, each one written by some well-known British expert in the particular field to be covered. In 1936 these articles were gathered together and published in two volumes, the first dealing with diseases of the respiratory tract, acute fevers, and cardiovascular disease, and the second dealing with diseases of the nervous and digestive systems, diseases of the blood, rheumatic and metabolic diseases, and

diseases of the kidneys and bladder. These volumes were so well received by the British medical public that there were new printings in March, 1937, and June, 1938. A new edition has now been published in the United States.

The list of contributors is a sort of Who's Who of the leaders in British Medicine, with such names as Lord Horder, Sir John Fraser, Sir E. Farquhar Buzzard, Wilfred Harris, S. A. Kinnier Wilson, John A. Ryle, Sir Arthur Hurst and J. W. McNee. On looking through some of the articles one finds much to commend, and about the only criticism that one can make is that the space was not always well

assigned. For instance, John Ryle was given only four pages in which to cover the treatment of "Some common digestive symptoms." Sir James Walton was given only six pages for the discussion of the "surgical treatment of peptic ulcer," and Hutchison had only four pages in which to discuss the treatment of constipation. Obviously no one could do justice to these subjects in such a limited space.

On the whole, however, the articles in these volumes are excellent. They are full of good ideas, and in many places one is pleased to find them so up-to-date.

Vitamins and Vitamin Deficiencies. By Leslie J. Harris, Philadelphia, Pa. Blakiston's Son & Co., Inc., 204 pp., 1938. Price \$2.50.

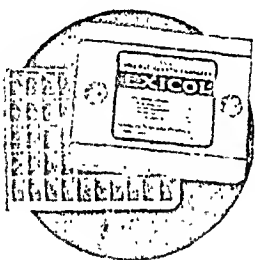
This is a splendid little book. As Dr. Harris says, an attempt was made to provide a "comprehensive synopsis" of the subject of vitamins. So often a synopsis of a subject is too brief and too incomplete to interest anyone who knows a good deal about the topic under discussion, and yet it should be possible to make a synopsis which contains everything of outstanding value and which can even tell the expert some things which he did not know.

Actually, in the space of 204 pages, Harris has presented an enormous amount of material. Every word counts and everything is made interesting. There are many good illustrations, and there are good bibliographies attached to each chapter. It is nice to find on pages 8 and 9, pictures of the eight outstanding early contributors to knowledge in regard to vitamins, from Lind to McCollum. We can heartily recommend this book for all those who do research or prescribe diets or teach.

Text-book of Nutrition. By J. A. Nixon and D. G. C. Nixon, London, Oxford University Press, 219 pp., 1938. Price \$6.00.

The Nixons start out by discussing the physiology of digestion and they continue with the subjects of food and metabolism, assessment of the state of nutrition, food requirements, vitamins, minerals, choice of foods, diet and income, diet and disease prevention, diet and disease production, diet and infection, diet and work, diet and physical efficiency, nutrition in disease and in lactation, and the effects of cooking. Obviously to cover adequately a huge field in 219 pages is impossible, and our only criticism of the book is that the various chapters are too short. They do, however, supply a great deal of information. There are a number of tables which supply information as to food composition, caloric content, and

Choosing a Happy Medium . . .



EXICOL

(Oleic Acid and Bile Salts)

The most recent researches* again emphasize the marked fat-intolerance displayed by patients suffering from gall bladder disease, and the satisfactory therapeutic results on a low fat diet and bile salts. Contrary to recent advocates of high fat therapy, it is pointed out that overstimulation of the gall bladder, produced by such high fat diets is undesirable.

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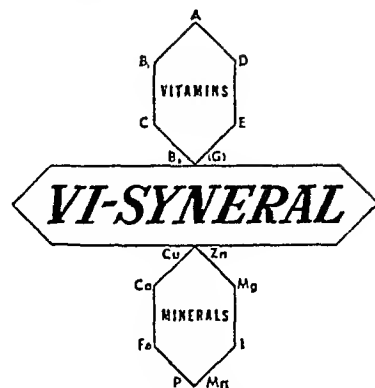
*Am. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

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THE vitamin and endocrine systems are inter-functional and improved glandular activity appears to occur with step-up in vitamin intake. Both the endocrines and vitamins unite in their influence on mineral metabolism. Inter-relationships of iodine, the thyroid and vitamin A consumption have been noted. Deficiencies of vitamins or low serum and tissue values for certain minerals produce atrophy of some glands and hypertrophy of others of the endocrine system.

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Sure, Barnett, *Endocrinology*, p. 575, Nov., 1938;

Bates, R. Alexander, *Amer. Med.*, Oct., 1936;

Kuhnau, Stepp, Schroeder, *The Vitamins and Their Clinical Application*, 1938, English Trans.;

Moriquand, G., *Lyon Med.*, 160:329, 1937;

Moinson, L., *Jl. de med. de Paris*, 57:407, 1937;

Abderhalden, E., *Med. Welt.*, 11:155, 1937;

Grab, W., *Munchen med. Wchnschr.*, 84: 605, 647, 687, 729, 1937;

Dorff, G. B., *Jl. Ped.*, 8:704, 1936, N. Y. Physician, Sept., 1938.

*Trade Mark Reg. U. S. Pat. Off.

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vitamin content. This is the sort of book that perhaps might be used for a nurses' course. It would hardly be complete enough for a dietitians' course.

The Special Pathological Anatomy and Pathogenesis of the Circulatory, Respiratory, Renal and Digestive Systems, Including the Liver, Pancreas and Peritoneum. By Horst Oertel. Montreal, Renouf Publishing Company, 640 pp., 1938.

One of the finest institutes of pathology in the world is to be found in Montreal, attached to McGill University and presided over by Dr. Horst Oertel. Anyone who has gone through

that magnificent institution will be particularly interested in possessing this textbook which Dr. Oertel has just published. In it he has endeavored to stimulate critical judgment and to excite further interest on the part of the student. The teacher of pathology will be interested because of the many evidences that Dr. Oertel has thought much in regard to the way in which pathology should be taught. The gastro-enterologist will, of course, be particularly interested in the section on the digestive system and the intestine. There is a good article on appendicitis and the way in which gangrene is produced.

Naturally, even in a book of 640

pages, the specialist can hardly expect to find his pet subject covered as completely as he would like it to be covered, and usually he will find certain gaps which he thinks should have been filled. For instance, on page 472 Dr. Oertel rather side-steps the extremely important question of the relation between gastric ulcer and gastric cancer. Unfortunately here and also throughout the book he tends to depend on quotations from others rather than on his own fine experience. The best books are always based mainly on the author's experience. Dr. Oertel apparently leans towards the theory that gastric ulcers originate in infarcts. He recognizes also the influence on the gastric mucosa of lesions in certain parts of the brain. The reviewer failed to find in the section on the colon any clear-cut discussion of the lesions of chronic ulcerative colitis. Carcinomas of the colon are also not well described.

On the whole, the book is interesting, and it will make a good addition to any medical library.

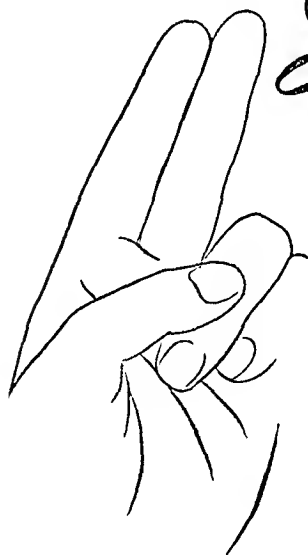
Functional Activities of the Pancreas and Liver. By Charles W. McClure. New York, Medical Author's Publishing Company, 318 pp., 1937.

It is difficult to review this book because it is hard to appraise its value. There is so much in it that is interesting, and it is written by an able man who has done a tremendous amount of work. It is well written, and it is well documented with many references. Certainly the book should be read by all those who are making a study of pancreatic and liver function and by all those who are interested in the analysis of human duodenal juice removed through a tube.

The reviewer has the feeling, however, as he reads the book, that it would have been much more valuable and convincing if Dr. McClure had only had at his elbow a sort of devil's advocate who would keep saying "Hold on there. Have you really proved that point?" He would have benefited greatly also if this devil's advocate had been a trained statistician who could have insisted that Dr. McClure have his chemical assistants plot all their data as distribution curves so as to see whether the distribution curve of figures from sick persons did not closely overlap the distribution of figures from apparently normal persons.

Anyone who knows how much the concentrations of bile and pancreatic juice can vary when these fluids are being recovered in pure form through a fistula can have little faith in his ability to learn much from studying these concentrations in juice removed from the duodenum after an unknown amount of dilution with gastric contents, duodenal secretions, and per-

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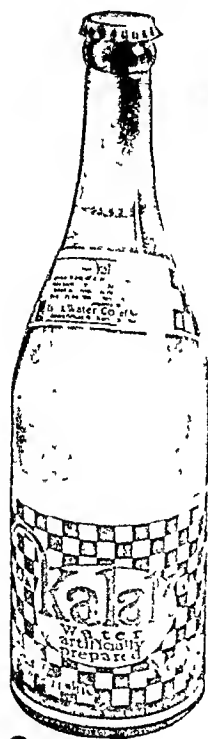
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*Fantus, B.: *Therapy of Disturbances Due to Heat*. J. A. M. A., Sept. 29, 1934, p. 990.

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haps the magnesium sulphate or other substance used as a stimulant. According to Dr. McClure's studies, magnesium sulphate stimulates not only the flow of bile but the flow of pancreatic juice, and naturally one would expect it to be very difficult to learn anything about a varying and unknown mixture of these two juices.

In many places throughout the book there are statements which are disturbing to an experienced clinician or a man who is statistically trained or a man who has some idea of what scientific logic should be. For instance, on page 184 one finds the statement, "determination of the state of liver

function by means of analysis of duodenal bile was carried out in 72 of the patients with migraine and in 65 showed the presence of hepatic dysfunction." This is such an important statement that one would expect it to be backed up with much more definite information. One would want to know how many of these patients showed liver dysfunction with the more recognized tests such as the Rowntree-Rosenthal or the galactose tolerance tests. Furthermore, the logically inclined person would wonder why it is, then, that migraine is not a severe symptom and accompaniment of definite cirrhosis of the liver. Actually,

the reviewer cannot remember ever seeing a case of definite cirrhosis of the liver in which migraine was troublesome.

On page 296 one finds a statement of Dr. Rowe's to the effect that "ablation of the female breasts in the adult human lowers the utilization capacity for galactose by 50 per cent." Any such statement in a book that is to be at all convincing should be backed up with figures showing how many cases were studied and what was the distribution of the data compared with those from normal women. To make such a statement without supplying the data is simply to cause the reader to distrust the whole book.

The reviewer's feeling, therefore, is that although an enormous amount of research work went into the book, the volume should be read only by men of a good deal of experience and critical sense.

Abstracts

SAHYOUN, PHILIP F. AND OPPENHEIMER, ALBERT.

Some Fresh Aspects of Appendicitis, a Joint Roentgenological and Histopathological Study. *Am. J. of Roent. and Radium Therapy*, Vol. 41, No. 2, pp. 185-197, Feb., 1939.

The object of this study is an attempt to correlate roentgenological and histopathologic findings in appendicitis. The method of examination consisted of a simple meal of barium and water and an examination of the appendix six hours later. If the appendix did not fill a second dose of barium was given the next morning followed by a dose of 2 cc. of castor oil. With this technique all normal appendices were visualized and most of the diseased ones revealed. A study of over 1000 normal appendices showed that a healthy appendix fills within six hours, empties before the cecum does, is uniform in caliber and dense and homogeneous in contrast. Free mobility and absence of tenderness are not essential points of a diagnosis of a normal appendix. The filling of the appendix is accomplished by pressure due to normal caecal peristalsis. The emptying of the appendix, however, is due to appendicular peristalsis. Such factors as severe constipation did not interfere with the emptying of the normal appendix.

Diseased Appendix: The most important sign in appendicitis, either acute or chronic, was the presence of stasis limited to the appendix. The whole colon or cecum may empty and yet the appendix will remain filled. Whenever stasis was found roentgenologically, histopathologic signs of

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chronic inflammation were demonstrable. The mucosal relief is definitely altered in inflammatory conditions producing rounded prominences bulging into the lumen.

Pathologic Study: The appendices were divided into two groups, the healed and the active. The healed group included those cases with obliteration of the lumen by scar tissue, cicatrization of the submucosa, scar formation in the muscularis of the mucosa and an increased amount of adipose tissue in the submucosa. The active group showed leukocytic infiltration of the muscularis. The authors maintain that where there is

a genuine active lesion in the appendix, an active process in the muscularis is a constant accompaniment of the lesions found in the mucosa and submucosa. In this study, wherever stasis occurred, lymphocytic infiltration and degenerative changes in the ganglion cells of the plexuses of Auerbach and Meissner occur. This view corresponds to the results of Aschoff's studies which correlated the signs of chronic inflammation in the intrinsic neuro-muscular system of the appendix with demonstrable motor disturbances. These histopathological changes were found both in acute and subacute appendicitis.

The authors feel that the motor disturbances associated with chronic inflammation may be an essential factor in the production of acute appendicitis. Thus, when a case is diagnosed as chronic appendicitis roentgenologically, appendectomy is certainly indicated to ward off an acute attack.

Henry H. Lerner, Boston, Mass.

CONNOTATIONS

H. J. SIMS, M.D.

Denver, Colorado

Claude Bernard's first job was as apprentice to a pharmacist. Soon after losing his job, he undertook to write a manuscript on a tragedy concerning Charles VI. This was rejected in 1834. Shortly before his death, he presented his manuscript to a friend and asked that it be published five years after his death with this statement: "It has been rejected and refused by M. Saint Mare Girdian." Nine years later it was published.

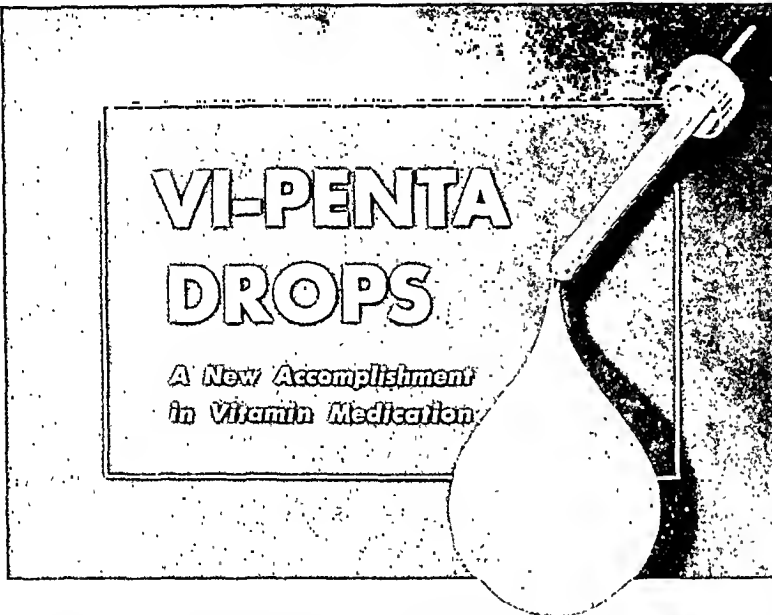
Professor Bottoni first used the galvano-cautery in 1872 in the treatment of hypertrophy of the prostate. It did not meet with general recognition until 1897 when Clark reported the cure of three cases.

In 1881, Sommenburg, aware of the unsuccessful autoplasmic methods, advocated extirpation of the bladder and union of the ureters to the urethral mucosa. Maydl suggested and Miluliez attempted transplanting the uterus into the rectum. One patient died from chloroform narcosis and the other patient passed urine and feces involuntarily.

Bezoars from animals were formerly supposed to have remarkable medicinal properties, especially as antidotes to poison. In man, three types of bezoars have been described. In 1854, Quain described the first case of phytobezoar in man. It consisted of a mass of cocoanut fibers and was found postmortem in the stomach of a young insane patient. In 1894, Outen described a bezoar in man due to eating persimmons.

Charles Byrne, an Irishman 8 feet and 4 inches in height, died in 1783 at the age of 22. Because of his gigantic features attempts by the medical profession to personally interview him led him to request that his body be buried in the sea. His skeleton is exhibited together with his boots in the Museum of the Royal College of Surgeons in London. The skeleton is 7 feet 7 inches tall and his boots are size 15½.

Until the middle of the sixteenth century, a text-book of medicine published in 1493 by Bartholomew was second only to the Bible in its number of printings. Bartholomew, in writing of epilepsy, stated that some cases were due to the brain and



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others to the stomach and extremities. He recognized epilepsy to be a disease of the brain; analepsia as arising from disease of the stomach; and eathalepsia as a manifestation of uncontrollable movements of the extremities. Concerning lethargy, he states that drunken men exhibit stupor because of perturbation of reason, or old men suffer it during the winter months from accumulation of phlegm or following some former sickness.

It is believed by many historians that Leonardo had a modern idea of the circulation of blood before its discovery by Harvey. As a corollary, he stated that the sea received water

from all the rivers while the sea of blood was the source of all the veins. He described the thyroid gland as a buffer, simply filling in space between the trachea and clavicle. He compared the voice box with that of a flute or organ pipe in the production of sound. He believed that the length and diameter of the trachea determined the pitch of the voice. He also believed the uvula aided in smelling. The intestinal tract was described as consisting of transverse and longitudinal fibers to give strength. The appendix acted as a safety valve for excess of gas. The gall bladder was thought to cleanse the liver of all impurities and to distribute vital

nourishment. He regarded the testes as the seat of emotion and described two canals in the penis, one for the urine and the other for the sperm.

Dr. Benjamin Rush, who lived 1745-1813, was active in the practice of medicine in Philadelphia during the epidemic of yellow fever, 1793-1803. He believed the disease was of domestic origin and thus differed from other physicians who believed it imported from other parts. He withdrew from the original medical society and with other colleagues who shared in his views organized the Philadelphia Academy of Medicine, a society which was short-lived. He advocated ten grains of calomel and ten grains of jalap at frequent intervals and also recommended copious bleeding. He himself, a victim of yellow fever, insisted he be given the same treatment.

Florus, born in 1751, was a distinguished anatomist of Guatemala. According to Van Patten, the English translation of Florus pamphlet in which is described the value of lizards in the treatment of cancer was published in 1782. A resident of Guatemala City who felt death near from cancer consulted the parish priest concerning the salvation of his soul. The priest recalled to memory an Indian suffering from cancer who was completely cured within a few days by a secret remedy, unknown except to the Indians. Upon request, the secret remedy was made known to the priest. He considered the treatment harmless and advised his friend to follow the information given by the Indians. According to the Indians, the head and tail of the lizard are quickly severed and the intestines and skin are immediately removed. The lizard is eaten while flesh is warm. Three lizards are to be eaten the first day; and within five days fever develops, followed by copious sweat. At this time five more lizards are to be consumed; within a few days, sloughing begins and the skin is replaced by healthy tissue.

Sylvius described intussusception as far back as 1614-1672. He described the malady as incurable though he suggested lead bullets or mercury be given with oil of almonds. Pare quoted Sanetus as having observed the recovery of a patient who was given three pounds of mercury by mouth. Sydenham objected to this form of treatment as he feared the mercury might extract the innate heat. Barbett advised in 1676 laparotomy for intussusception.

THEWLIS, MALFORD W.

A New Antispasmodic Drug in Gastro-Enterology. Medical Times, 67, 12-13, 1939.

This report presents the results obtained on a single case study. The

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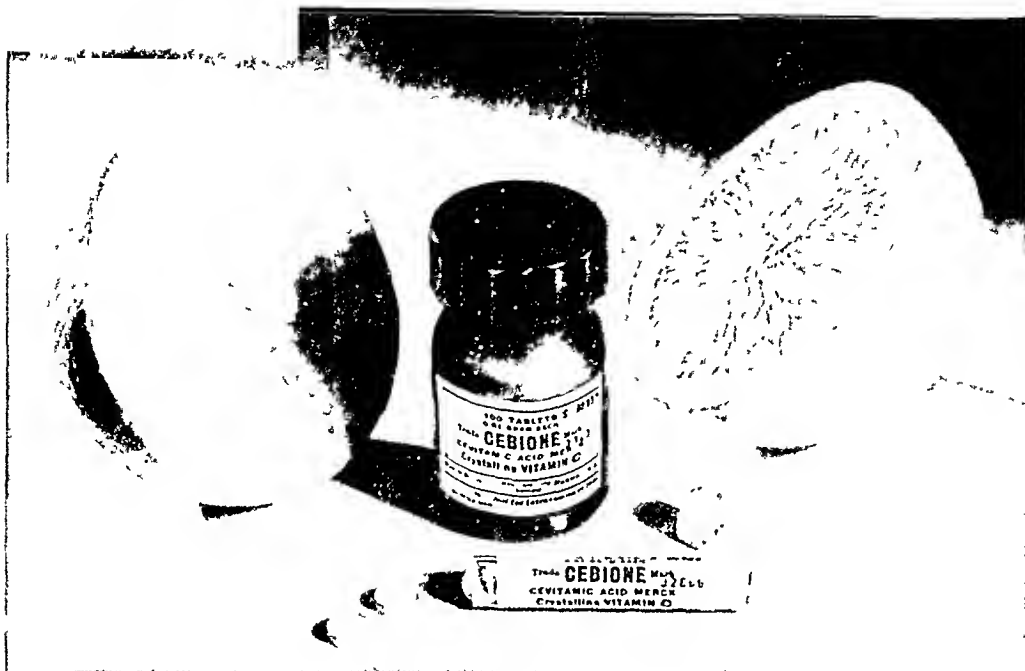
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subject was a woman who had been suffering from a severe post-prandial abdominal pain for a period of seven weeks, which pain did not respond to treatment with the usual opiates. Relief was finally obtained by means of Beta-diethylaminoethyl diphenylacetate-HCl administered in oral doses of 75 milligrams after each meal.

Franklin Hollander.

BENEDICT, MITCHELL M.

"Peptic Ulcer and the Larostidin Treatment." The Military Surgeon, Nov., 1938.

Doctor Benedict, in a recent article commenting upon the effects of the Larostidin treatment, reached the

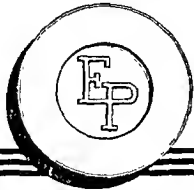
following conclusions: The parenteral administration of histidine monohydrochloride in 132 cases of gastro-intestinal disorders, 112 of which were peptic ulcer, was followed by rapid remission of clinical symptoms and radiologic evidence of improvement. Regulation of the diet and the mode of living need not be as strict as with other types of treatment, but a reasonable diet and avoidance of undue mental and physical exertion should be observed to secure the most satisfactory results from the histidine treatment. The prompt improvement with the histidine treatment permits the patient to become ambulant early in the treatment and short-

ens the period of hospitalization to one month. Patients with peptic ulcer tolerate a liberal diet, in the histidine treatment, even during the crisis. The incidence of recurrence was reduced in cases of peptic ulcer receiving the histidine treatment, and all recurrent cases responded satisfactorily to a second treatment. In tuberculous enterocolitis, the parenteral administration of histidine has been followed by rapid remission of diarrhea and spastic abdominal pain. The general condition and the appetite improves. Cases of peptic ulcer complicated by other diseases respond satisfactorily to the histidine treatment. The complicating disease should be treated at the same time. The histidine treatment has been found of value in the treatment of gastro-intestinal ulcers other than peptic ulcer. The parenteral administration of histidine in other diseases, particularly those of the respiratory tract, may be found of value. The daily parenteral administration of histidine monohydrochloride has been found the therapy of choice in gastro-intestinal ulcers.

FORSELL, GOSTA.

The Role of the Autonomous Movements of the Gastro-Intestinal Mucous Membrane in Digestion. Am. J. of Roent. and Radium Therapy, Vol. 41, No. 2, pp. 145-165, 1939.

Comment: Forsell, ever since 1923, has maintained that the mucous membrane of the gastro-intestinal tract has the power of autonomous movement so that it can adapt itself for various purposes in the mechanical phase of digestion. His studies which have been pursued for many years have finally led him to the conclusion that such activity does take place. He is also firmly convinced that other movements of the mucous membrane play a part in the absorptive function. Over a period of time he has obtained mucous membrane reliefs from animals and humans by injecting formalin into the vascular system immediately after death. In this way, he determines certain patterns which he maintains are consistent in all animals. Since the advent of gastroscopy, we have been trying to confirm the presence of autonomous movements of the mucous membrane but without success. Likewise, the textbook description of the conformation of the mucosa in the stomach has likewise not been constantly observed. Recently, by modifying our gastroscopic technique and using very little insufflation or not at all, if possible, we have had some degree of success in visualizing certain anatomic features of the mucous membrane pattern which Forsell has so accurately described. Since in this



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The superiority of Tincture Metaphen in these two respects and in length of action is empha-

sized by a recent report.* On the oral mucosa, Tincture Metaphen was found to reduce bacterial count 95 to 100% within five minutes after application; to cause only a slight irritation in some cases, no irritation in the others; and to have, in substantial excess of any other antiseptic tested, a duration of action of two hours.

Tincture Metaphen does not affect surgical instruments or rubber goods. It is quite stable when exposed to air. The distinctive orange stain which Tincture Metaphen produces clearly delineates the field of application, yet may be easily and quickly removed from skin or from linens

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Tincture Metaphen is supplied in 1-ounce, 1-ounce, 16-ounce and 1-gallon bottles. Tincture Metaphen, *Untinted*, is also available for use where a safe and efficient antiseptic is indicated, but where staining is undesirable. It is available at all pharmacies in the same package sizes as the tinted Tincture Metaphen. Abbott Laboratories, North Chicago, Illinois.

*Meyer E., and Arnold L.; *Amer. Jour. Digest. Dis.*, v. 5, p. 118, September, 1933

★ ★ ★

TINCTURE METAPHEN

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paper he maintains that the mucous membrane pattern is determined by the quantity and consistency of the food which is in the stomach, we are about to attempt a series of studies wherein gastroscopy will follow upon the ingestion of food particles. In this manner, we hope to determine whether or not the mucous membrane adapts itself to its contents.

Review: Forssell maintains that the mucous membrane is influenced both by the degree of contraction of the muscle wall and the consistency and form of the contents of the digestive canal in respect to the forward passage of the ingesta.

In the phase of maximal contrac-

tion with an empty lumen, the mucous membrane forms what he calls a "initial relief" which is specific in each portion of the digestive tract. On the other hand, where the canal is distended, the mucous membrane forms a "final relief." In the stomach, colon and rectum the membrane folds disappear in this latter phase. However, in the small intestine, the transverse folds persist, even in the presence of marked distention. With some contraction of the muscular wall the macroscopic folds of the mucosa form a "working relief" which is produced without altering the diameter of the tube in response to the type of ingesta present. When the contents are

fluid as in the small intestine, the relief is uniform and regular. Where soft contents are present, "small digestive chambers" are formed by projecting folds. When the contents are solid, or a mixture of solid with semi-solid, the mucous membrane encloses the particle almost entirely in a cup-like chamber and may surround the particle even though the main lumen of the gut remains free. Wherever gas exists in the digestive tract, the mucous membrane forms smooth cavities with regular contents. In this way, we really have two mechanisms independent of each other for movement in the digestive canal. The muscular tube and its sphincters distribute the contents to the various portions of the digestive tract. The mucous membrane forms small mechanical workshops which provide for the individual mechanical processes of digestion.

Forssell shows a large number of illustrations of his anatomical preparations demonstrating a number of the functional variations of the mucous membrane relief. To appreciate a description of his exhibits, the article must itself be read. His portion on the stomach is extremely interesting, particularly to the gastroscopist by whom direct visualization and proof of Forssell's theory of autonomous movements in the mucous membrane of the stomach can be obtained, if true.

Henry H. Lerner, Boston, Mass.

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The mucous membrane relief is a new method of visualization and proof of Forssell's theory of autonomous movements in the mucous membrane of the stomach can be obtained, if true.

Forssell, Smith, E. and
Tall of A. Modern Medical
Treatment, Wm. Wood & Co.,
New York, 1921, p. XVI



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WHAT THE EXPERIMENTAL SURGEON HAS LEARNED ABOUT ULCER

In a recent article Dr. Frank Mann (Minn. Med., 20:753) summarized most of what is known about the experimental production of ulcer. His statements were so concise and to the point that they are well worth repeating here.

1. Ulcer rarely follows diversion of bile from the duodenum, but acute ulcers are frequently found in the condition of jaundice following obstruction of biliary outflow.

2. Acute duodenal ulceration frequently follows the complete loss of pancreatic secretion from the body, but rarely occurs if secretion of the pancreas is prevented by obstruction to the outflow of pancreatic juice.

3. Ulcer occurs in a small percentage of instances in which the duodenum is removed.

4. Ulcer frequently occurs in the duodenum if the bile and pancreatic ducts are drained into the terminal ileum.

5. Drainage of the entire duodenal content into the terminal ileum causes ulcer to form in almost every instance in the jejunum or ileum which has

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been placed in the position previously occupied by the duodenum.

6. The site at which the ulcer develops is so remarkably constant that it is possible at operation to indicate accurately where the ulcer will form.

7. By changing the angle of the loop of gut anastomosed to the stomach it is possible to change the site where the ulcer will occur and to indicate this area at the time of operation.

8. Varying the size of the opening through which the gastric content is expelled changes the rate at which the ulcer forms. The ulcer occurs more rapidly with the smaller opening.

9. Injury to the motor mechanism of the stomach, such as making an hour-glass stomach, delays but does not prevent the development of ulcer.

10. Resistance of the intestinal mucosa to ulcer decreases progressively from the pylorus to the colon.

11. The loop of intestine anastomosed to the stomach can be turned at different angles in relation to its blood supply without affecting the site at which the ulcer develops.

12. An incision can be made repeatedly within short intervals of time in the loop of intestine containing an ulcer opposite the lesion and

the ulcer observed. The incision heals but the ulcer does not.

13. An ulcer will show evidence of healing within a few hours after it has been completely protected from contact with the gastric content.

14. An ulcer will heal slowly if the duodenal content is drained so it will pass over the lesion.

15. An ulcer will heal slowly following a gastro-enterostomy.

16. When an ulcer is made to heal by preventing the gastric content from passing over it, another ulcer usually develops in the efferent loop of intestine in the pathway of the gastric content of the gastro-enteric anastomosis made to drain the stomach. It should be noted that the site of the new ulcer was subjected to the same condition as the site of the original.

17. The healing process in an ulcer only partially protected from contact with the gastric content is irregular and slow, with many complications, such as reformation of a portion of the ulcer and hemorrhage.

19. During the healing process the newly formed tissue is very delicate and can be washed out of the ulcer with unbelievable ease.

20. Removal of all the fundic mucosa except a narrow tube for the passage of food greatly delays the

formation of the ulcer but does not prevent its occurrence.

21. If an isolated fundic pouch is drained by an isolated loop of intestine, ulcer will occur in the intestinal loop.

22. If an isolated pyloric pouch is drained by an isolated loop of intestine ulcer does not occur.

23. Ulcer will occur after section of the nerves to the stomach.

24. A diet of coarse food will increase the rate at which an ulcer develops, while a liquid diet retards the rate of ulceration.

25. Patches of jejunum, transplanted into the wall of the fundic portion of the stomach, do not become ulcerated.

26. Patches of jejunum, transplanted into the lesser curvature of the pyloric portion of the stomach, frequently do become ulcerated.

27. Patches of the fundic region of stomach, transplanted into the wall of the jejunum or ileum, produce ulceration in the intestinal mucosa.

28. Areas from which the mucosa is excised heal more rapidly in the fundic region than in the ulcer-bearing area of the pyloric region.

29. All the major complications of ulcer, as noted in the human, have been observed in the experimentally produced lesion.

AS ONE PHYSICIAN TO ANOTHER...

In Treating Constipation, This is What 9 Physicians Out of 10 Would Say . . .

New habits of elimination, new dietary habits are the basis of most successful treatment. However, in aiding in the re-establishment of such habits, a bland pure mineral oil may often be most helpful. And now, in light of recent studies upon the effects of Vitamin B-1 in the gastro-intestinal tract, this important food factor may be an essential in restoring normal tones to the neuromuscular mechanism of the intestines.

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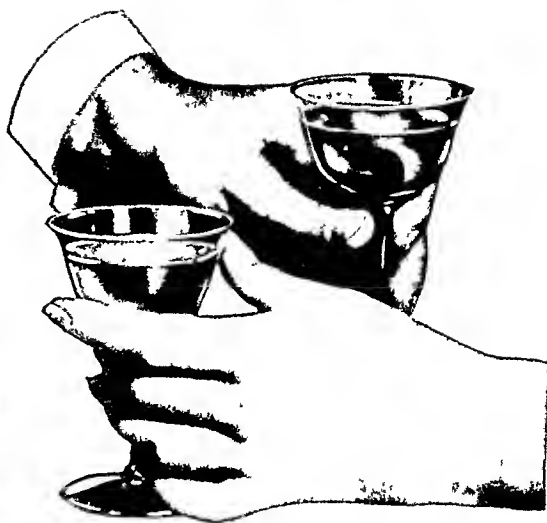


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30. Finally, it should be emphasized that these experimentally produced ulcers cannot be distinguished grossly or microscopically from ulcer as seen in man.

This large amount of accumulated data indicate conclusively that chronic peptic ulcer can be produced experimentally by interrupting the chemical coördinating mechanism whereby the acid gastric content is diluted, buffered and neutralized as soon as it leaves the stomach. Ulcer occurs in a mucosa subjected to the action of the acid gastric content and unprotected by the acid-reducing mechanism. Ulcer does not occur in the absence of acid or in the presence of this mechanism for reducing acidity. The motor mechanism of the stomach is important in determining the site of the lesion the ulcer occurring in the area on which the acid gastric content first impinges upon leaving the stomach and the rate of progress of the lesion, the ulcer forming more rapidly where the acid gastric content is expelled with greater force. The force with which the content of the stomach is expelled is modified by the size of the opening of emergence, being greater with smaller opening."

MEULENGRACHT, E.

Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia. Am. J. Med. Sci., Vol. 197, No. 2, pp. 201-214, Feb., 1939.

Former investigators have shown that the anti-anemic factor in the stomach (Castle's intrinsic factor) is not found in the pepsin and hydrochloric acid-producing fundus portion, but in the pyloric portion and duodenum, and it must be secreted by the pyloric glands and the histologically identical Brunner's glands. Meulengracht examined the stomach and duodenum of eight cases who had suffered from pernicious anemia. His microscopic examination revealed considerable gastritic changes in the fundus portion with atrophy of the glands and disappearance of parietal and chief cells. But the gastritic changes were less pronounced in the pyloric portion, and the glands seemed relatively well preserved; no histologic changes could be demonstrated in Brunner's glands. The histologic changes were thus most marked in the region of the hydrochloric acid-producing and pepsin-producing fundus glands, but less marked in the pyloric gland region, and entirely absent in the vicinity of Brunner's glands. It is also expedient to draw attention to Goldhamer's experiments which indicated that it was the volume of the gastric fluid which was reduced in pernicious anemia, while the anti-anemic activity per unit volume was the same as under normal conditions. Therefore it is possible that a functional insufficiency exists. On the

GASTRITIS

AS A PRECURSOR OF

PEPTIC ULCER

"One may reasonably postulate that gastritis is the precursor of gastric ulcer on the basis of combined clinical and histopathologic observations."

Eusterman, Year Book of Medicine, 1938, page 703.

A rapidly accumulating mass of clinical evidence points to an ancestry of gastritis for peptic ulcer. This view is now accepted by many noted gastroenterologists.

In any case, gastroscopy and bar-relief X-Ray studies show that gastritis is a common complicating factor in ulcer and an accompaniment of almost all gastric ailments.

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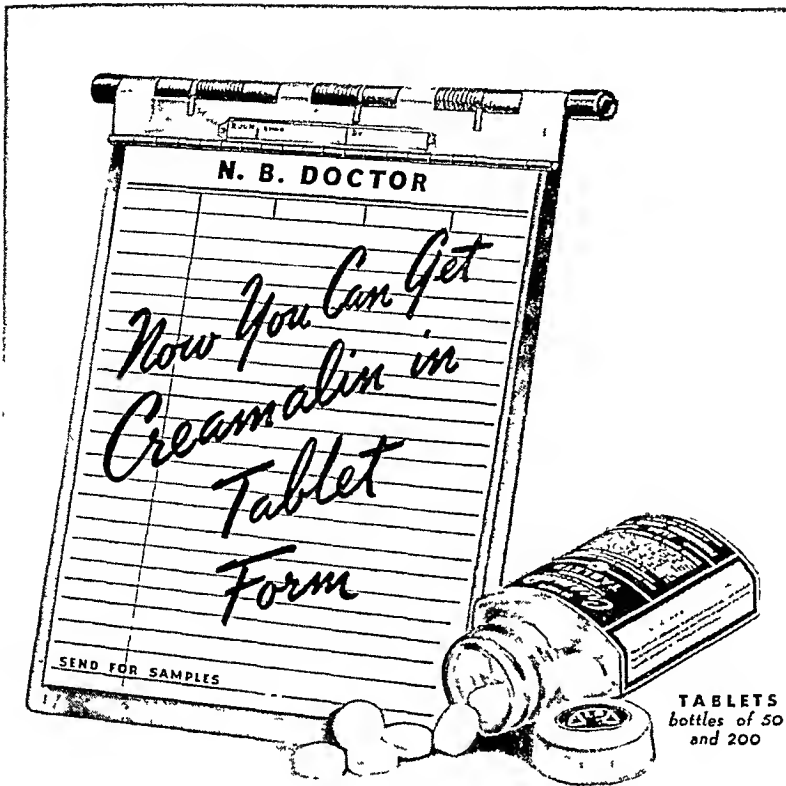
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other hand, we must consider the possibility that processes in the intestine are wholly or in part responsible. The author believes that two facts have been established: 1, That the anti-anemic factor of the stomach is produced by the pyloric gland organ; but, 2, that a histologic investigation shows that the pyloric gland organ is relatively intact in pernicious anemia.

Franz J. Lust.

PACK, GEORGE T. AND MCNEER, GORDON.

Analysis of End-Results Following Experimental Radiation Therapy of Gastric Cancer. A report of 268 cases. Am. J. Roent. and Radium Therapy, Vol. 41, No. 3, pp. 391-403, March, 1939.

In an excellent, well-prepared, scientific, and well-formulated study, the authors analyze a series of cases of gastric cancer which were subjected to radiation therapy, both external and internal, by the roentgen ray, by the radium element pack—preoperatively and postoperatively.

From their work, they concluded that the present methods of radiation therapy may prolong the life expectancy of the patient with inoperable gastric cancer but is of no curative value. Cancers of the lesser curvature respond best to irradiation. However, their survival period is less than that of cancers in the media, fundus and cardia. The addition of radiation therapy to surgical procedures prolongs the life expectancy of the patient.

Henry H. Lerner.

BELLOMO, ALDO.

Treatment of Gastric and Duodenal Ulcer with Intravenous Injections of Bromine and Atropine. Minerva medica, 11, 489-93, 1938.

Five cases each of hyperchlorhydric gastritis and gastric ulcer were treated with atropine and bromohydroxyethylamine intravenously. The doses were 1 milligram of the former and 10 cc. of a 25 per cent soln. of the latter, corresponding to 0.77 grams of bromine. Results were successful.

Franklin Hollander.

TEMPLETON, FREDERIC E. AND SCHINDLER, RUDOLF.

Roentgenologic and Gastroscopic Studies in Chronic Gastritis and Peptic Ulcer. Am. J. of Roent. and Radium Therapy, Vol. 41, No. 3, pp. 354-367, March, 1939.

The authors present a correlated study between the roentgenologic diagnosis of gastritis in the presence of peptic ulcer and the gastroscopic observations and diagnosis of gastritis.

The pathology of gastritis they base upon the work of Faber and Block, wherein two general types of

chronic gastritis were found to exist—the hypertrophic and atrophic. However, the fact that normal histology of the gastric mucosa has not been clearly defined invalidates to some extent this criterion.

The clinical diagnosis of gastritis is as yet awaiting definition until sufficient autopsy material correlated with gastroscopic material has been collected. Gastroscopically, gastritis is divided into three types—the superficial type is defined as the mucosa which shows few hyperemic spots without gross mucosal defects. The atrophic type shows grayish-green spots and at times the blood vessels of the submucosa can be visualized. The mucosal membrane pattern is very thin. The hypertrophic type shows large, swollen, velvet-like, verrucous, nodular and segmented folds with very shallow ulcerations. Roentgenologically, the demonstration of gastritis is limited to the hypertrophic form. They conclude, therefore, that chronic gastritis can only be diagnosed gastroscopically.

Another finding which seems of interest is that gastritis is not always present gastroscopically in the presence of gastric or duodenal ulcers. Likewise, in a few scattered instances, there was no evidence of microscopic ulcers in these cases.

Comment: This is another instance wherein an attempt is made to

compare two types of observations, namely, gastroscopic or roentgenologic, without having any accepted and established criteria for either set of observations. Until there has been a more specific correlation between pathology and gastroscopy, such comparisons must be weighed carefully before being accepted. The authors themselves realize this by raising the question as to whether the pathologist can differentiate between normal and abnormal gastric mucosa, whether the changes seen by the gastroscopist always indicate gastritis, and whether gastritis can exist without being visible through the gastroscope.

With our present state of knowledge, the answer to all three of these questions is still indefinite.

Henry H. Lerner.

HASEGAWA, TAKURO.

Hormonal Action of the Spleen on Gastric Juice Acidity. Arbeiten aus der medizinischen Fakultät Okayama, 6, 68-71, 1938.

For these experiments, rabbits were provided with Pavlov pouches and subsequently subjected to splenectomy. Following removal of the spleen the total acidity of the pouch secretion was increased; administration of spleen extract to these animals, however, reduced the acidity to its normal level. Atropine exerted a

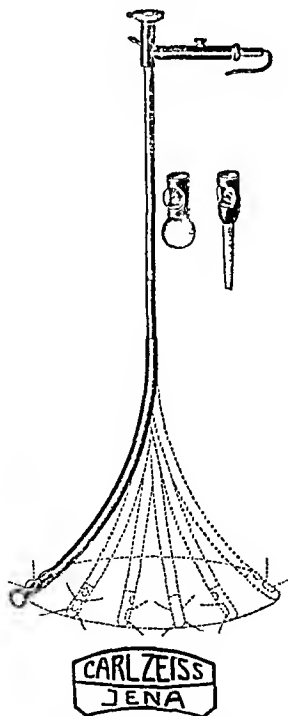
similar effect. These results indicate that the spleen yields an atropine-like hormone which exerts a vagus-paralyzing action on the secretory mechanism of the stomach.

Franklin Hollander.

PICKHARDT, OTTO C. AND RAFSKY, HENRY A.

Problems Presented by Lesions of the Right Quadrant. J. A. M. A., Vol. 109, No. 25, pp. 2048-2053, Dec. 18, 1937.

Pickhardt and Rafsky stress the fact that appendicitis is such a comparatively common disease, that the symptoms referable to the right lower quadrant are often ascribed to an inflammatory process of the appendix when in reality the lesion is in the cecum or the terminal part of the ileum. Not infrequently patients with nonspecific granuloma or regional ileitis have an appendectomy performed and subsequently, when the symptoms recur, a pathologic process in the ileum is discovered. Patients with symptoms due to cecal stasis, spasm of the cecum or other lesions in this region are often subjected to the removal of the appendix only to have a recurrence of the clinical syndrome, perhaps in a more persistent form. The cecum may be the site of a benign or malignant tumor or an



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*An interesting Editorial on this material appeared in the March issue of The American Journal of Digestive Diseases, entitled, "Aids to Normal Bowel Function," authored by Dr. J. Arnold Bergen of Rochester, Minnesota. Reprints will be supplied upon request.

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inflammatory or edematous process, infectious, parasitic or allergic in origin, which may give rise to a rather confusing clinical picture. It is a fact that the usual physical and laboratory examinations do not always reveal the correct diagnosis. Special methods of investigation may be necessary, particularly a study of the small intestine. Pickhardt and Rafsky stress the importance of duodenal installation of barium and taking films every one or two hours. Most of their diagnosis were due to a very skillful roentgenological examination. The reported cases contain such rarities as a mucocoele of appendix or angioneurotic edema with visceral manifestations. A case with symptoms of appendicitis could be detected as gastro-intestinal allergy. Scratch tests revealed the allergens. The roentgenological examination enabled the diagnosis of cases as an intussusception of ileum into the cecum, with papilloma of cecum, or of diverticulitis of the cecum or of neoplasms of the cecum. Several cases of regional ileitis are among the material and show that due to exact examination we are able to find this condition comparatively frequent. Pickhardt and Rafsky emphasize that a more frequent study of the small intestine as a means of detecting lesions of the terminal part of the ileum and the cecum should be encouraged. Those conditions do not always need surgical interference but can be treated medically. The surgical treatment of lesions of the right lower quadrant will vary as to the pathologic process found. If marked inflammatory edema on regional ileitis is present, an ileocolostomy, with short-circuiting of the affected part by means of healthy intestine well away from the lesion, is to be preferred, with possible subsequent resection.

Franz J. Lust.

STETTEN, DEWITT AND ABELOFF,
ABRAM JOSEPH.

Observations on the Clinical Picture and Therapy of Diverticulitis of the Colon. Journal of the Mount Sinai Hospital, Vol. IV, No. 6, March-April, 1938.

Diverticulitis of the colon is not an uncommon condition and should always be thought of in a patient, especially one after middle life, suffering from an acute abdominal disturbance. It is a very serious malady, often with a protracted morbidity and a high death rate.

The positive diagnosis of the disease is still very difficult notwithstanding many clinical and pathological studies, based on a wealth of material, that have been made on the subject in the past thirty-four years. Actually the only moderately definite

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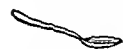
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preoperative diagnostic pointer is the X-ray examination by barium elysma, and this can only be used in a quiescent stage of the disease.

Of the eighteen cases of diverticulitis operated upon, all with obvious surgical indications, thirteen recovered and five died. They may be grouped pathologically:

1. Peridiverticulitis and penetration into mesentery with localized peritonitis.

2. Peridiverticulitis and perforation with localized intraperitoneal abscess.

3. Peridiverticulitis, with or without perforation, with spreading peritonitis.

4. Peridiverticulitis and perforation with diffuse fibrinopurulent peritonitis.

5. Sigmoiditis and perisigmoiditis with inflammatory tumor producing stenosis of the intestinal lumen, in one of which there had been a previous perforation, localized abscess and secondary fecal fistula above the stenosis.

6. Sigmoiditis and perisigmoiditis with dense adhesions to the urinary bladder.

Stetten emphasizes that ultraconservationism should be the therapeutic watchword. Medical treatment should be instituted at first, if possible. If progressive peritonitic or obstructive symptoms and signs or the suspicion of malignancy force a resort to surgical intervention, the least radical operative procedure compatible with the findings should be adopted. In certain instances deep X-ray therapy over the diseased area seems to be beneficial.

Franz J. Lust.

EGGERS, CARL.

Gastro-enterostomy. Ann. of Surg., Vol. 108, No. 1, July, 1938.

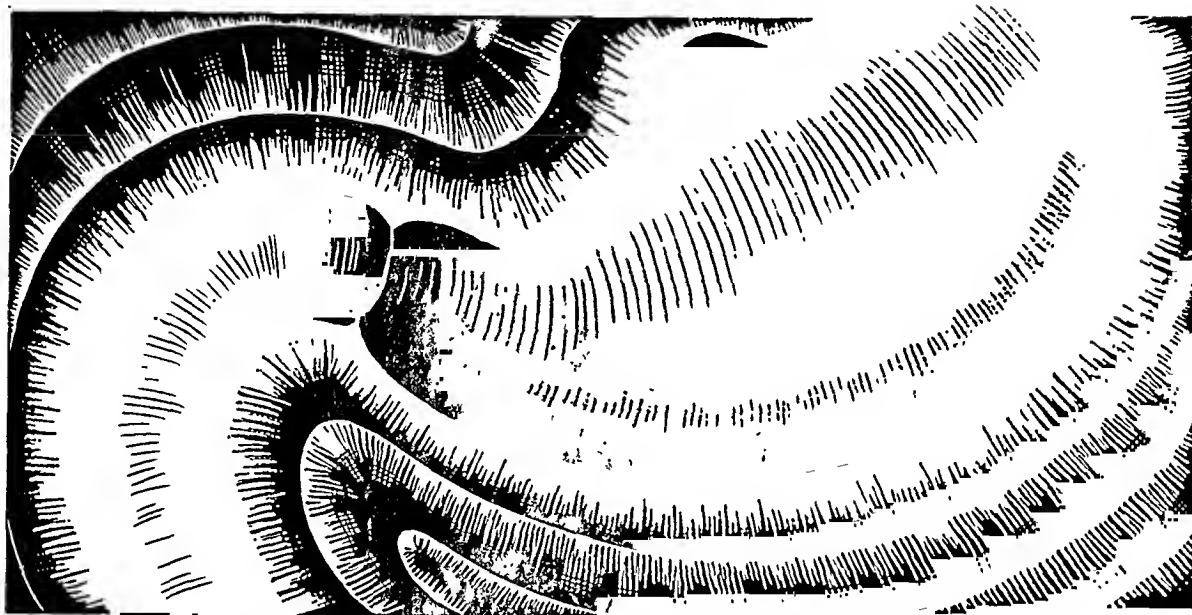
Eggers reports his findings with gastro-enterostomy in 84 cases. In 12 of these cases the operation was performed for inoperable carcinoma. The indications for gastro-enterostomy in 72 cases: chiefly for ulcer symptoms—39, chiefly for symptoms of obstruction—17, and combined symptoms of ulcer and obstruction—16 cases. Three of the 72 cases, or 4.1%, died as the result of the operation. Eggers gives the indications for gastro-enterostomy as:

1. In cancer of the pyloric end of the stomach in which radical operation is impossible on account of extensive local involvement metastases, or poor general condition. If successful, it relieves symptoms and prolongs life for a while.

2. In all benign obstructions of the pylorus due to extensive adhesions, scar contracture from ulcer, stenosis following operations for perforation, or after unsuccessful pyloroplasties.

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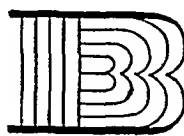
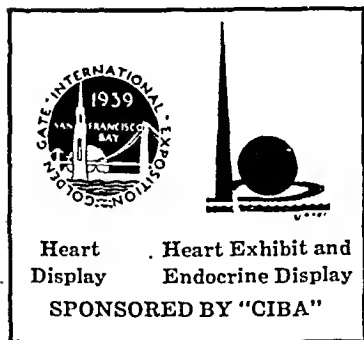
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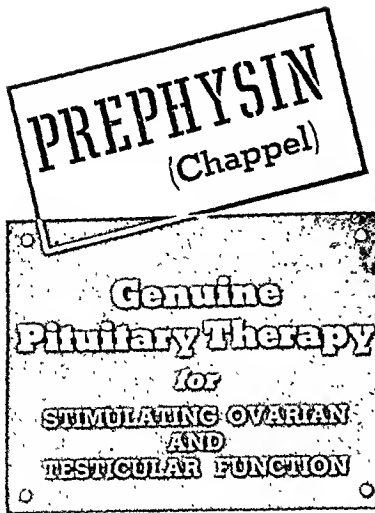
**Einhorn, M., AM. J. DIG. DIS., April, 1938.

Literature and Additional Indications Upon Request

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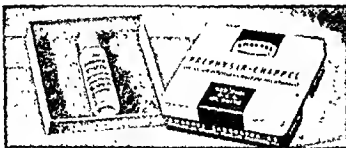
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*Sevringhaus, E. L., "Endocrine Therapy in General Practice," 1938.



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after repeated attempts at medical cure have been unsuccessful.

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b. As a secondary operation where a previous conservative operation has failed or where gastrojejunal or jejunal ulceration has developed.

3. In duodenal ulcers:

a. When repeated hemorrhages, especially massive hemorrhages, have not been controlled.

b. After failure of conservative operations.

c. For intractable pain.

d. Possible for gastrojejunal or jejunal ulcer.

Franz J. Lust.

RICHARDSON, HENRY B.

Simmonds' Disease and Anorexia Nervosa. Arch. Int. Med., Vol. 68, pp. 1-28, Jan., 1939.

The diagnosis of Simmonds' disease in life is uncertain. Emaciation, appearance of age, gonadal atrophy, and depression of the basal metabolic may all be the result of starvation.

Six cases are presented. In three the diagnosis of Simmonds' disease was made at some time clinically, in the other three the clinical resemblance was close to Simmonds' disease. In the course of years all were proved to be anorexia nervosa. Amenorrhoea, depressed basal metabolic rate were found in all. The cases were indistinguishable clinically from autopsy proved cases of Simmonds' disease in the literature. An added difficulty is that the anterior pituitary may be destroyed without producing the clinical picture of Simmonds' disease. Occasionally, however, the diagnosis of pituitary insufficiency can be made with the finding of change in the sella turcica roentgenographically.

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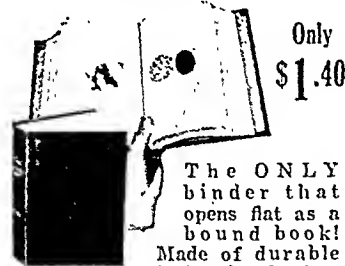
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A MESSAGE TO HOME CANNERS FROM THE CANNING INDUSTRY

● Every year, in various regions of the country, a considerable amount of the produce from thousands of small orchards and gardens is preserved for future use by canning in the home. Despite much that has been written on the subject (1), outbreaks of botulism from improperly heat processed home-canned foods continue to be reported.

To eliminate the possibility of botulism from their products—specifically those foods of the “non-acid” type—home canners should take a page from the experience of commercial canners. Through considerable research, the American canning industry has scientifically established the necessary processing requirements for products of this character. For non-acid foods, modern canners employ only recommended process time and temperature schedules (2) known to be adequate to destroy the heat-resistant spores of *clostridium botulinum* whose growth produces the toxin which causes the deadly type of food intoxication known as botulism.

Brief comment on the heat-processing requirements of common foods might be in order. In general, foods or food products may be classed into two groups according to their acidity, i.e., the “acid” and “non-acid” classes with pH values below and above 4.5, respectively. The acid foods include tomatoes and the common fruits. These foods are not favorable to the growth of *clostridium botulinum* and consequently they may be safely processed at 212°F., or the temperature of boiling water.

The non-acid products, however, present a special processing problem. Such products

—meat, fish, fowl, milk and most common vegetables—can be adequately processed only at temperatures above 212°F. As the records indicate (1) botulism in home canned foods may result from processing non-acid foods in boiling water. Safe canning of these foods in the home, therefore, requires the use of properly operated “pressure cookers”—identical in principle with the “retorts” used by commercial canners—which will permit the use of a process under steam pressure. Usually 10 lbs. steam pressure is used in these cookers which corresponds to a processing temperature of 240°F.

Home canners desiring to pack non-acid products should obtain a copy of United States Department of Agriculture Farmers Bulletin No. 1762. In this bulletin are described the necessary equipment, precautions, and time and temperature processing schedules required for the safe canning of non-acid foods in the home. If the necessary equipment cannot be obtained and the recommendations contained in the above bulletin cannot be faithfully followed, some means of preservation of non acid products other than canning should be sought.

In the interests of public health, it is our sincere hope that home canners may soon become educated to the necessity of steam pressure processes for non-acid foods. Experience dictates that only by processes of this type, with a time and temperature schedule suitable for each particular product, can botulism from non-acid home canned foods be effectively controlled and ultimately eradicated.

AMERICAN CAN COMPANY

230 Park Avenue, New York, N. Y.

1 1934 J Home Econ 26 365 376
1935 Amer J Pub 25, 301 313
1935 J Amer Med Assn 105, 205
1936 Food Research 1, 171 198

2 1937 National Canners Association,
Washington, D. C.
Bulletin 26 L, 3rd Ed

We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles. This is the forty-eighth in a series, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research.

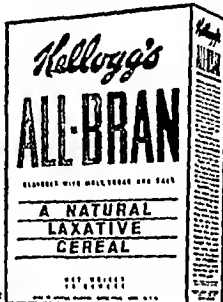


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A Study of *Bacterium Necrophorum* in Chronic Ulcerative Colitis and of the Effect of Sulfanilamide in Treatment*

By

G. M. DACK, Ph.D., M.D., J. B. KIRSNER, M.D., L. R. DRAGSTEDT, Ph.D., M.D.

and

ROBERT JOHNSON

CHICAGO, ILLINOIS

THE significance of *Bacterium necrophorum* as an etiological agent in chronic ulcerative colitis has been discussed in a number of reports from these laboratories (1, 2, 3 and 4). Our attempts to reproduce the disease in experimental animals by means of this organism have so far met with failure. However, an impressive amount of evidence, varied in nature but incriminating *Bact. necrophorum*, has gradually accumulated in our studies, and this will be analyzed, together with the data obtained in the present investigation. Virulent strains of *Bact. necrophorum* produce a uniformly fatal infection in rabbits when injected subcutaneously. Sulfanilamide (5) when properly administered has been found to cure such infections. Treatment must be commenced on the third day and continued for a considerable period. The lesions gradually regress and the organisms disappear. In view of this experience, it appeared desirable to investigate the action of sulfanilamide in cases of chronic ulcerative colitis in man. If a therapeutic result should be obtained, additional evidence with respect to the role of *Bact. necrophorum* ought to be secured.

During the course of our work, a paper appeared by Bannick (6) and his co-workers in which they reported the treatment of 12 patients with chronic ulcerative colitis with sulfanilamide and neoprontosil. Nine patients had uncomplicated cases, whereas three were complicated. They concluded that "certain cases of chronic ulcerative colitis seem to offer a favorable field for the use of neoprontosil or the cautious administration of sulfanilamide."

Feder (7) treated 3 patients with chronic ulcerative colitis with 30-40 grains of sulfanilamide daily in divided doses. The treatment was carried out for two weeks and after a rest period of two weeks was continued. He concluded that there was no apparent benefit from its use. Brown, Herrell and Barger (8) used neoprontosil (oral) in the treatment of patients with chronic ulcerative colitis. They gave 4 to 5.32 gms. in 5 doses for 10-14 days, followed by 2.64 gms. daily for 10-14 days, after which a full course using the larger dose was given. They concluded that early cases with mild to moderate involvement of the bowel offer the best field for this form of therapy. Collins (9) of the Cleveland Clinic used sulfanilamide in 11 cases, both by mouth and retention enema and apparently obtained excellent results in 8 cases.

EXPERIMENTAL

The isolation and identification of *Bact. necrophorum* in cultures secured from the lesions of chronic

ulcerative colitis is a difficult task and is not always accomplished in a single undertaking (1, 2). The organism is non-sporulating and not easy to cultivate. It is a strict anaerobe and colonies die on exposure to the air for even a few hours. A rich blood agar medium is used and since this does not inhibit the growth of other intestinal organism, *Bact. necrophorum* may be missed if a sufficient number of cultures are not taken. A medium favoring differential growth, such as is available for typhoid and dysentery bacteria, would facilitate the study considerably. Furthermore, it must be recognized that specimens taken from the colon at proctoscopic examination contain the fecal flora as well as bacteria from the lesions in the intestinal wall. Not infrequently *Proteus* is found, and when motile organisms of this type are present it is practically impossible to recover *Bact. necrophorum*, since the former organisms spread over the surface of the plate. In a few cases the persistence of *Proteus* has entirely prevented the isolation of *Bact. necrophorum*. Usually, however, *Proteus* is transient in large numbers and may not be encountered when further cultures are taken from the same bowel in the course of a few days or weeks. A severe diarrhea may also hinder the isolation of *Bact. necrophorum* because of excessive contamination from the fecal stream.

The stools of all patients studied were routinely examined for parasites, and in this series none were encountered. A search was also made for dysentery bacilli by streaking eosin-methylene blue and desoxycholate-citrate agar plates with specimens taken at proctoscopic examination. No dysentery bacilli were found, although many specimens were examined from each patient.

The normal habitat of *Bact. necrophorum* in nature has not been established. Since the organism has been found in necrotic lesions of the mucous membranes throughout the body in both man and animals, we felt that, in view of our present experience in culturing this organism, a thorough search should be made for it on the mucous membrane of the normal colon. We therefore took cultures at proctoscopic examination from the normal colons of 99 patients, following a technic previously described (1, 2). Cultures also were secured from lesions of the colon in patients with diseases other than chronic ulcerative colitis. See Table I. Usually only one culture was taken from lesions in the colon of these patients. It is difficult to culture such lesions and avoid gross fecal contamination, which interferes with the isolation of *Bact. necrophorum*. If more cultures were taken, undoubtedly *Bact. necrophorum* would have been found in a larger number of these cases. It is significant, how-

*This study was supported in part by a grant from the Committee on Scientific Research of the American Medical Association.
From the Departments of Bacteriology and Parasitology, Medicine and Surgery of the University of Chicago.
Submitted March 17, 1939.

ever, that this bacterium does not frequent the mucosa of the normal colon.

The finding of *Bact. necrophorum* in ulcerating lesions of the colon in patients who do not have chronic ulcerative colitis is in complete accord with our previous experimental observations. We have shown, by traumatizing the colon of animals by curettage or electric cautery, that a necrotic lesion develops and, after a period of time, *Bact. necrophorum* may be isolated from the lesion (1, 3, 4). Such lesions, however, eventually heal. Henthorne, Thompson and Beaver (10) of the Mayo Clinic isolated an organism indistinguishable from *Bact. necrophorum*, which they call *Bacteroides funduliformis*, in pure culture from four

TABLE I

Incidence of Bact. necrophorum in patients without ulcerative colitis

	Positive	Negative	Remarks
Normal Colon	0	99	104 cultures
Carcinoma Rectum and Rectosigmoid	1	10	
Malignant Polyp Rectum	1	0	
Benign Polyp Rectum	0	1	
Lymphogranuloma Inguinale	1	0	2 positive cultures—granular, bleeding mucosa below stricture
Sonne Dysentery (?)	0	1	
Chronic Flexner Dysentery	0	1	2 cultures—normal mucosa at last exam.
Inflammatory Stricture Sigmoid with Benign Polyps (Biopsy)	1	0	6 positive cultures in 10 attempts
Proctitis	2	2	
Anal Fissure	1	2	-
Radium Necrosis of Bowel	0	1	
Squamous Carcinoma Cervix with Rectal Bleeding	0	1	
Diverticulosis of Colon	0	2	
Diverticulitis of Colon	0	2	
Total Number of Cases	7	122	

cases of hepatic abscess. Three of the patients had carcinoma of the rectum and in the fourth the primary pathological lesion was unknown. They also isolated this organism from a fecal (?) fistula in a patient with a carcinoma of the sigmoid flexure. Our studies in man (Table I) as well as those in experimental animals (1, 2, 3, 4) have shown that *Bact. necrophorum* is present when there is ulceration and necrosis of the colon mucosa, regardless of the cause. These observations would explain the origin of the organisms in the liver abscesses described by Henthorne, Thompson and Beaver as undoubtedly coming from the colon. It is particularly interesting that *Bact. necrophorum* may be found so frequently in abscesses in pure cultures, whereas in the bowel or in other ulcerations of mucous membranes it is present in mixture with many different species of bacteria. Apparently it has certain pathogenic properties which make it possible for it to invade and leave the other bacteria with which it is usually associated.

Thirty-eight patients with chronic ulcerative colitis

were studied in this series. *Bact. necrophorum* was found in 27 of these patients in cultures taken at proctoscopic examination. In 11 cases *Bact. necrophorum* was not found; 7 of these patients were in periods of remission. Only one specimen was taken in 5 of the 11 patients with negative cultures, and only 2 cultures were taken in 3 others in this group. See Table II.

Of this group of 38 patients, 10 received sulfanilamide therapy. See Table II. The daily dosage varied from 1.8 to 6 grams, although 3 to 3.6 grams daily was the usual amount given. Three of the patients, E. K., H. A. and I. D., received neoprontosil, E. K. and H. A. for a period of three weeks, and I. D. for a period of one week. These patients were continued on a low residue non-laxative diet, and the only medication given was sulfanilamide. All patients under sulfanilamide therapy were seen on an average of every 4-7 days. *Bact. necrophorum* was not found in 2 cases. In one of these, J. Van S., the bowel had healed at the time the bacteriological examination was made. In a second patient, W. C., *Proteus* contaminated the plates when the discase process was most active. Patients M. F. and J. Van S., who received no sulfanilamide, were included in the table as examples of the fact that healing occurs in this disease without drug therapy.

Although our series of patients treated with sulfanilamide is small, the study has been carried over a sufficient period of time to indicate that sulfanilamide does not influence the healing process markedly. In some cases the lesions improved soon after administration of the drug. This improvement was of mild degree and disappeared when treatment was discontinued. Whether this result was coincidental or an effect of the sulfanilamide therapy is still to be evaluated.

During the course of treatment two patients developed skin lesions, one having two lesions on the face and the other having a generalized toxic drug rash. The skin lesions in both cases disappeared following discontinuance of the drug. There was some evidence that both of these patients had been exposed to the sunlight. In these two patients subsequent administration of the drug did not bring about a return of the skin lesions. Some of the patients complained of various systemic reactions, such as described for this drug, but in no case were there any serious effects. Blood counts and hemoglobin determinations were made frequently. A slight to moderate decrease in the red blood cell count was noted in several instances.

During the course of sulfanilamide therapy two of the patients developed colds. Both patients were taking full doses of sulfanilamide and had been under this treatment for a period of some weeks when they developed colds. This observation is of interest in view of the fact that sulfanilamide therapy has been found ineffective in the treatment or prevention of virus diseases.

DISCUSSION

In discussing the role of *Bact. necrophorum* in chronic ulcerative colitis, many facts must be considered (11). The disease attacks young and old, but the majority of cases occur in the second to fourth decades of life. It affects people of all races and those of different dietary habits. The number of cases in

the population is small. The lesions begin in the rectum in 95 per cent of cases and remain localized to the rectum in only 20 per cent. Epidemics of this malady do not occur; usually there is only one case in a family. The properties of *Bact. necrophorum* fit particularly well these epidemiological facts. In the first place the natural habitat of this organism is thought by some workers to be the mucous membranes.

TABLE II

Incidence of Bact. Necrophorum in chronic ulcerative colitis

Patient	No Cultures	Positive	Negative	Proctoscopic Findings
J. P.	1	1		Typical
B. S.	1		1	Granular, bleeding mucosa
M. F.	8		2	Granular mucosa—slight bleeding—1 culture— <i>proteus</i>
E. P.	3	3		Typical
B. H.	1	1		Positive culture obtained also granular bleeding mucosa—at autopsy from material in bowel
Mrs. G.	1	1		Typical
M. N.	2	1	1	Granular mucosa—no bleeding
E. P.	5	4	1	Typical—2 cultures <i>proteus</i>
M. B.	1	1		Typical
P. Z.	2	2		Typical
R. W.	1		1	Granular mucosa—no bleeding
E. R.	2	1	1	Granular mucosa—little bleeding
F. G.	1	1		Typical
S. S.	2		2	Granular mucosa—slight bleeding
I. S.	4	4		Typical
N. G.	1		1	Typical
C. S.	1		1	Finely granular mucosa—no bleeding
M. F.	9	2	7	Slight to no changes with 5 negative cultures and one positive culture
M. S.	2		2	Mild changes with second culture
J. Van S.	3		3	No changes—cultures after colon healed
D. S. L.	3	1	1	Typical—1 culture— <i>proteus</i> overgrowth
L. S.	8	4	2	Colon healed with negative cultures—3 <i>proteus</i> overgrowth
A. Z.	1	1		Typical
S. K.	3	D	2	No bleeding with negative cultures typical otherwise
L. G.	4	2	2	Mucosa practically normal
D. L.	18	4	14	Granular, bleeding mucosa with positive cultures
B. N.	20	8	7	Usually typical—5 <i>proteus</i> overgrowth
D. Lo.	26	12	14	Usually typical changes
J. W. A.	31	28	3	Hypertrophied—bleeding mucosa—slight bleeding with 2 negative cultures
M. S.	23	9	14	No changes with 10 negative cultures
J. M.	25	7	16	Usually no bleeding with negative cultures—several cultures contaminated
E. K.	23	15	7	Usually granular bleeding—1 culture <i>proteus</i> overgrowth
W. C.	23		4	Usually typical—19 cultures: <i>proteus</i> overgrowth
I. D.	5	1	4	Inflamed bleeding mucosa with much purulent exudate
H. A.	7	4	3	Typical
Mrs. P.	1	1		Mild changes
E. G.	1	0	1	Normal—culture after colon healed for 1 year
K. K.	1	1		Finely granular mucosa—no bleeding
				Negatives
				No patients No cultures
				5 1 culture
				3 2 cultures
				1 3 cultures
Total	38 cases	Positive=27 Negative=11		

It appears in necrotic lesions experimentally produced in the colon of otherwise healthy animals. However, we have not succeeded in isolating it from the normal intestinal wall. *Bact. necrophorum* appears as an opportunist and establishes itself when the ulcerative process is initiated. The chronicity of the disease would suggest that the infectious agent is of low virulence and that immunity, if developed, usually is not strong or lasting. Our knowledge of *Bact. necrophorum* is in keeping with this assumption, since the many strains which we have isolated from the colons of patients suffering with chronic ulcerative colitis have uniformly been of low virulence when injected subcutaneously into rabbits. Furthermore, with virulent strains we have never been able to produce immunity in rabbits. These animals injected with non-colitis virulent strains and treated with sulfanilamide until recovery are just as susceptible as normal rabbits to reinfection with the same strain.

The pathologic anatomy characteristic of infections caused by *Bact. necrophorum* in the skin of rabbits resembles in a general way the picture of chronic ulcerative colitis in man. The relatively slight pathogenicity of *Bact. necrophorum* and its failure to produce colitis when instilled into the isolated colon of monkeys is in harmony with the fact that the entire colon discharges from chronic ulcerative colitis patients produced a similar negative result and the well-known fact that the disease itself is rarely, if ever, transmitted even by closest contact.

In some of the patients where the disease appeared to be established in a chronic form, there was a tendency for the bowel to heal under continued sulfanilamide treatment, although exacerbation of the process occurred following withdrawal of the drug. This lack of immune response in both patients and animals with experimental infections is in keeping with a chronic disease of this type.

There is no doubt that *Bact. necrophorum* is a pathogenic organism, although ordinarily it appears to lead a saprophytic existence. In addition to the numerous examples in the literature, we have encountered a few cases (not ulcerative colitis) in which *Bact. necrophorum* has been found in metastatic lesions producing low grade chronic infections that continued for months or years. We have recently seen a patient with a fistula in the breast, through which there was considerable drainage. This condition had been present for six years. *Bact. necrophorum* was recovered in almost pure culture from the purulent discharge. In certain other cases, the organism was found in abscesses in pure culture. From some of these abscesses strains have been recovered which are indistinguishable from those which we have isolated from the colon of patients with chronic ulcerative colitis.

The evidence which suggests that *Bact. necrophorum* plays an essential role in chronic ulcerative colitis may be summarized as follows:

1. When the seriously diseased colon is isolated from contamination by the fecal stream, as by end ileostomy, aerobic organisms disappear from the colon discharges, the flora becomes almost entirely anaerobic and *Bact. necrophorum* predominates (1, 2, 3). Such an isolated colon remains diseased often for years with intermittent periods of quiescence and exacerbation.

During the periods of quiescence, *Bact. necrophorum* usually disappears, only to become plentiful again with each new exacerbation.

2. *Bact. necrophorum* has been found in the great majority of cases of typical ulcerative colitis when appropriate methods for its detection have been used, but is not found in the normal colon.

3. The organism is pathogenic for rabbits, producing in them local abscesses and systemic infection, and also for man as indicated by its isolation in pure culture from liver abscesses, from persistent purulent sinuses, from empyema thoracis, and from a portal thrombus in a patient who died of ulcerative colitis.

4. Specific antibodies for this organism have been found in the blood in cases of chronic ulcerative colitis and not in the blood of normal individuals (2), indicating that the organism is implicated in some way in the mechanism of the disease, either as a cause or as a secondary invader.

5. Examination of the literature indicates that it is very similar to, if not identical with, *Bacillus* or *Bacteroides funduliformis*, which has been repeatedly found associated with necrotic lesions of the mucous membranes in man, and with *Bacillus necrophorus*, which is thought to cause various necrotic lesions in wild and domestic animals.

The occasional isolation of *Bact. necrophorum* from ulcerating processes in the colon other than chronic ulcerative colitis does not necessarily lessen its significance in this disease. It may well be that the organism is present in small numbers in the normal alimentary tract of man and monkeys and that it requires

some additional factor, producing necrosis of the mucosa, to furnish conditions suitable for its proliferation. Once this occurs, the organism seems capable of continuing and extending the process.

SUMMARY

Bact. necrophorum was not found in cultures taken at proctoscopic examination from the normal colon of 99 patients. It was found in 7 of 28 cases in which there was disease of the colon other than chronic ulcerative colitis. *Bact. necrophorum* was isolated from 27 of 38 patients in various stages of chronic ulcerative colitis. Ten of these 38 patients were treated in the acute stage of the disease with sulfanilamide. Sulfanilamide did not appear to hasten healing very markedly, although mild to moderately severe cases showed slight improvement temporarily. There is a tendency for exacerbation of symptoms on withdrawal of the drug. Although experimental *Bact. necrophorum* infections in rabbits may be cured with sulfanilamide, this bacterium does not disappear from the diseased colon of patients taking this drug. After healing occurs, *Bact. necrophorum* is usually absent. A discussion is given in the paper concerning the possible significance of *Bact. necrophorum* in chronic ulcerative colitis.

The authors wish to express their appreciation to Dr. Walter L. Palmer for the opportunity to study many cases of chronic ulcerative colitis on his service and for much helpful advice and criticism, and to Drs. George F. Dick and William H. Taliaferro for advice and help in analyzing the data.

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The Hydrogen Ion Concentration of Human Feces, Urine and Ileac Dejecta

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THOROUGH studies have been made on the reactions and hydrogen ion concentration of human feces passed both normally and after the administration of laxatives. Early observations on the reactions of feces were made by the use of such substances as extract of cochineal, methyl orange and lacmoid, if the reaction was suspected of being acid. If an alkaline reaction was suspected, an indicator such as phenolphthalein, rosolic acid or curcuma was

used. The general conclusion to be drawn from this early work is that the reaction of human feces is near the point of neutrality. The early work of Howe and Hawk (1) indicated that the pH of human feces was from 7.01 to 8.77, but that there was practically always an alkaline reaction. The extensive work of C. S. Robinson (2) showed the reaction of human feces when the individuals concerned were following a mixed diet to be between pH 7.0 and 7.5. In these investigations, the hydrogen ion concentrations were measured electrometrically, using the general technic

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and apparatus described by Clark. Robinson (3) used the quinhydrone electrode in a subsequent investigation and obtained data which were in agreement with data obtained from his former investigations.

We thought it would be of general interest to determine the pH of human feces by means of the glass electrode after the administration of castor oil, sodium phosphate and magnesium sulfate, and to compare

TABLE I

Results of determination of the pH of urine and feces (determined with the glass electrode)

Patient	Time of Determination	pH		Laxative Used
		Feces	Urine	
1	12:00 M.	6.89	5.42	Sodium phosphate
	1:15 P.M.	7.02	5.16	
2	4:30 A.M.	—	5.29	Sodium phosphate
	4:44 A.M.	7.12	—	
	7:00 A.M.	7.10	5.15	
	10:00 A.M.	7.08	5.18	
	11:30 A.M.	6.70	—	
3	6:30 A.M.	7.30	6.00	Sodium phosphate
	11:30 A.M.	7.17	—	
	2:45 P.M.	7.22	5.32	
4	8:10 A.M.	7.62	5.03	Magnesium sulfate
	9:45 A.M.	7.19	—	
	11:15 A.M.	7.33	—	
	3:50 P.M.	—	5.07	
	—	—	5.27	
5	10:15 A.M.	6.32	5.18	Castor oil
	12:15 P.M.	6.48	5.11	
	12:30 P.M.	6.36	—	
	12:45 P.M.	6.27	—	
	1:30 P.M.	6.56	5.15	
	2:46 P.M.	—	5.58	
	4:00 P.M.	6.35	6.66	
6	8:40 A.M.	6.42	—	Castor oil
	9:00 A.M.	6.69	—	
	1:00 P.M.	—	5.76	
	11:00 P.M.	6.61	—	
	2:00 A.M.	6.00	—	
	3:00 A.M.	6.53	—	
	8:00 A.M.	6.30	—	
	9:00 A.M.	5.88	—	
	10:00 A.M.	6.18	6.11	
	3:45 P.M.	—	6.18	
	5:20 P.M.	—	6.66	

these pH measurements with those obtained from ileal fluids obtained from ileas dejecta. Also, we thought it of value to determine if there were any comparable trends of variation in the hydrogen ion concentration in the feces and urine.

Accordingly, the urine and feces of individuals who were in the hospital receiving preparation for a surgical operation on the colon, or for a roentgenogram of the colon, were studied. Individuals who are to undergo an operation on the colon commonly receive from 2 to 4 drachms (7.66 to 15.50 Gm.) of a saturated solution of sodium phosphate several times a day until the intestines have been fairly well emptied of feces. As soon as the bowels of the patients began to act after administration of the laxative the feces and urine were collected. In the table, patients 1, 2 and 3 had received sodium phosphate; patient 4 had received castor oil. As may be observed in the table, no specific or definite generalizations can be made. The pH varied in the feces through moderately wide limits, in each case as well as among cases. The general trend of the pH of the feces was definitely acidulous. However, the degree of the fecal acidity bore no definite relation to the degree of acidity of the urine.

Ileac dejecta from two patients collected at frequent intervals for a period of from four to six hours had a range of pH values from 6.35 to 6.76, a range of pH much more constant than that which was observed in the feces after the administration of laxatives.

It seems reasonable to surmise from the data in the table that when the feces are passed in liquid form, as the result of the administration of purgatives, the pH of the liquid portion will be approximately the same as that of the ileal fluids. There does not seem to be any association of the trends of pH in the urine and feces.

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The Present Status of the Radiologic Diagnosis of Duodenal Ulcer

By

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DUODENAL ulceration is one of the most common affections of the gastro-intestinal tract. The first reports of this condition were described as early as the 16th century, and were based upon autopsy findings. It was not until the development of the roentgen ray that the condition was accurately diagnosed in the living subject. The ulcer niche defect was radiologically demonstrated as early as 1910 (1), and since then the X-ray diagnosis of duodenal ulcer has been popularized on an anatomic basis. Later, in addition to the ulcer niche, various deformities of con-

tour of the duodenal bulb have been emphasized as being due to ulceration. In the early roentgen period, the diagnosis was not made very frequent, owing to the difficulty encountered in demonstrating the ulcer niche defect. In 1914, Cole (2), pioneered the radiologic demonstration of bulbar deformities by serial roentgenography. Since then there has appeared a greater impetus than heretofore, to diagnose this condition. These marginal deformities are produced largely by spasm in the early cases and by contraction and retraction, due to sclerosis of the duodenal wall in the advanced cases. An interesting characteristic

of the deformity is that the ulcer itself is usually of small size and shallow, and that the marginal deformity is always out of proportion to the pathologic change in the duodenum.

The roentgen diagnosis of duodenal ulcer has now attained a high degree of accuracy. However, all roentgenologists do not obtain the same degree of diagnostic accuracy. It is noteworthy to point out that, a rather high percentage of cases are recognized by the characteristic marginal deformities, when the older methods of examination were utilized.

Duodenal ulceration is the most common of all peptic ulcers. It occurs in about 70 per cent of cases, and is more often observed in males than in females. The relative proportion is shown in a collection of 1107 cases, in which 876 were males and 231 females (3). The condition is commonly observed between the second and fifth decades of life. It must be emphasized that a thorough and painstaking history will often reveal that the initial development of the ulcer frequently begins during adolescence.

In the development of the ulcer, four stages are radiologically recognized. The initial stage is shown as a localized edema, with or without the presence of an ulcer niche. The ulcer crater may be so shallow that the characteristic niche defect cannot be seen at this time. There is usually some bulbar irritability, and localized spasm. In the second stage, the ulcer crater is deepened by the swelling and piling up of the mucosal folds, and is recognized as a persistent ulcer niche defect. Marginal deformities are also demonstrable, as a result of spasm. The third stage is recognized by thickening of the duodenal wall, which produces a retraction of the bulb toward the ulcerated side. This stage is also characterized by the convergence of the mucosal rugae toward the ulcer. At a later period, an eccentricity of the duodenal bulb in its relation to the pyloric sphincter may be seen. A frequent complication is the formation of an accessory pocket, as a result of a slow chronic perforation. In the fourth stage, the thickened indurated duodenal wall produces a shrinkage in the caliber of the lumen, forming a narrow rigid canal.

Duodenal ulceration is usually single, but may be multiple. Multiple ulcers are now more commonly observed than previously, since the innovation of the more modern roentgen technic, which enables the roentgenologist to visualize the walls of the bulb with greater clarity and ease. The roentgen incidence of multiple duodenal ulcerations, secured from numerous reported series of cases, varies from 16 to 60 per cent (3).

Duodenal ulceration may be associated occasionally with gastric ulcer. The incidence of this coexistence according to statistics varies from 3.3 to 19.3 per cent (3).

Duodenal ulcers usually occur within the first portion of the duodenum. They are more often localized in the basal portion, in the mesial aspect, and are rarely observed on the margins. The niche is more often located nearer the lesser than the greater curvature side of the bulb. The vast majority of the ulcers occur on the anterior or posterior walls of the duodenum, with perhaps a slight preponderance on the posterior wall.

There is a general impression among the profession that the radiologic diagnosis of duodenal ulcer is made

with ease. This is undoubtedly true in the moderate advanced or late cases in which marked marginal deformities are demonstrable. In the early stages of the development of the ulcer, when marginal deformities are absent, the diagnosis becomes increasingly more difficult for the radiologist. With the advance of the newer radiologic principles in the examination of the duodenal bulb, it is now possible to detect early cases with a high degree of accuracy. Despite the tremendous volume of study on the roentgen diagnosis of duodenal ulceration, the addition of new radiologic phenomena based upon morphologic changes has received but little attention. This is attested by the fact that a patient with an early ulceration may be seen by a number of radiologists and obtain many different diagnoses. In recent years great strides have been made toward the recognition of duodenal ulceration in its early stages. The new radiologic procedures have a distinct advantage in educing finer details which have hitherto been masked by the opaque material. With improved equipment and increasing experience in recognizing ulcer niches, the degree of reliability and the number of cases accurately diagnosed will be tremendously increased. The roentgen projection of the ulcer niche defect is not a new sign, but its demonstration because of its location has been difficult to portray without the use of the compression technic. The niche, although formerly considered a rarity, is now a very frequent finding, and is pathognomonic of ulcer. However, the presence of the niche is not always essential for the diagnosis of this condition.

In as much as it is generally believed that the roentgen recognition of duodenal ulcer offers little difficulty, it might be pointed out that there are many instances in which minimal and early changes are not easily discernible. These cases now make up a large percentage of patients seeking medical attention, and it behooves the roentgenologist to meticulously examine the duodenal bulb more closely in order to depict the earlier changes which are recognized as being due to ulceration. Recently, attention has been directed to the earlier recognition of duodenal ulceration which is not usually recognized by many roentgenologists (5). The gastro-enterological roentgenologist is keenly aware of the fact that there has been a large number of cases, clinically diagnosed as duodenal ulcer, which could not be confirmed by the usual radiologic method of examination. It should be emphasized that the early recognition of ulceration depends largely upon the visual acuity of the examiner, his knowledge of the minute pathologic changes, and his experience in being able to detect them in the early stages.

In 1913 (4), Forssell laid the groundwork for the intramural studies of the digestive tract by his researches on the gastric and duodenal mucosa, which now forms the basis of the modern methods of examination and diagnosis for peptic ulceration. Formerly the roentgenologist was not required nor was he equipped by experience to report on the finer details of the morphological changes occurring in duodenal ulceration. By utilizing the compression technic the duodenal bulb reveals a characteristic pattern. The mucosal pattern shows from 3 to 5 shallow longitudinal rugae, running parallel with the bulb, ending abruptly at the juncture with the 2nd part of the duodenum. In the case of ulceration, the mucosal rugae are obliterated in the involved area as a result of

edema. In later stages or during the healing stage the rugae may be seen to converge toward the ulcer.

In addition to the demonstration of the ulcer niche defect and the marginal deformities, an early manifestation of ulceration is presented by a localized area of edema, which is recognized as producing a ringed or negative area on compression, with the formation of a fragmented bulb (5). The demonstration of the fragmentation sign greatly augments the radiologic armament of the roentgenologists. The fragmentation sign is best demonstrated by the use of compression under the fluoroscope. In this procedure the excess of opaque medium is ejected from the normal duodenal bulb, thus forming a skeletonized cap of lesser density, but of more or less homogeneity. In early ulceration the above technic will show a fragmentation or splitting up of the barium in a regular pattern, which can be repeatedly seen at different intervals during the examination. The duodenal bulb will be broken up into a number of petal-like shadows resembling a rosette, which radiate mesially toward the ulcer. The radiologic demonstration of the rosette figure is produced by approximating the walls of the bulb by means of manual compression. Pressure over the ulcerated area and surrounding edema, because of the fact that the anterior and posterior duodenal walls cannot be brought evenly and intimately together, tends to distribute the opaque medium in a petal-like fashion. When the bulb is allowed to refill completely, this fragmentation sign cannot be seen, unless compression is re-applied. Marginal deformities are not usually observed at this stage. The duodenal bulb appears normal in every respect, and unless one is familiar with this phenomenon, the condition will be entirely overlooked. It must be emphasized that fragmentation of the bulb may be the only sign that presents itself, especially in the early stages of duodenal ulceration. This sign unfortunately has not received the attention it deserves, and its real diagnostic significance has not been clearly established until emphasis was directed to it in the recent literature. The associated localized spasm also aids in producing the roentgen picture of fragmentation. The progressive clinical roentgenologist now recognizes these early changes in a large percentage of cases.

The niche defect is radiologically portrayed by a small dense, circular or oval opaque spot, due to the deposition of opaque medium in the ulcer crater. This niche is usually surrounded by edema, which produces an area of lessened density which is revealed by a translucent halo or ring-wall around the ulcer. After the ejection of the excess of barium, the niche stands out in relief and is almost invariably accompanied by spasm on the greater curvature side, opposite the ulcer. When the bulb is completely filled, the ulcer niche is hidden by the density of the opaque meal. According to statistical evidence, the roentgen incidence of niche findings varies from 13 to 98 per cent.

Every active ulcer of the duodenum which extends more deeply into the wall of the bulb, produces some alteration in the radiologic appearance of its shape and contour. The deformity is due to a combination of organic and functional changes. However, the predominant component of the deformity is usually due to spasm. In extreme cases almost the entire lumen may be obliterated, or the bulb may be transformed into a narrow rigid canal, while in the less severe forms the bulb assumes a variety of shapes. These marginal deformities are generally more obvious than the niche itself.

The association of spasticity of the pylorus is a common accompaniment of ulceration. The close proximity of the ulcer to the pyloric sphincter frequently involves the pylorus by direct extension. With involvement of the pylorus the gastric symptoms are markedly exaggerated.

The healing of duodenal ulcers is not as easy to demonstrate as the healing of gastric ulcers. In those instances in which an ulcer niche is visualized in the original examination, healing may be demonstrated by the diminution in size of the niche or by its complete elimination. The disappearance of spasm and irritability of the bulb may also be observed. Converging rugae and slight irregularities due to scar formation may be seen. In chronic ulceration with marked marginal deformities, healing may be difficult to disclose, while in the intractable variety, the deformities do not change from year to year.

SUMMARY

Since patients having digestive disturbances submit themselves for examination at an earlier period than in former years, it is important that the roentgenologist focus his attention upon the early morphological changes in the duodenum, which have hitherto often been overlooked.

The early radiologic changes presented are due to slight edema, producing the fragmentation sign on compression, and the ring-wall sign or translucent area, also due to edema. Later, the ulcer niche defect, spasm, irritability and marked deformities of the duodenal bulb are observed.

A careful radiologic study, with particular emphasis on the compression technic aids in demonstrating the early signs of duodenal ulceration and enables the roentgenologist to make an accurate and early diagnosis.

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The Intestinal Phase in Urologic Disease

II The Role of the Colon in Uroinfections

By

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IN another paper (1), attention was directed to the embryologic, anatomic, and physiopathologic relationship that exists between the intestinal and the urinary systems. It was also shown that the colon, as well as the entire intestinal tract, could act as a wide potential portal of entry for organisms into general circulation, or act as a serious focus of infection.

Reiman (2) also considers "the various inflammatory states of the digestive tract such as appendicitis, cholecystitis, colitis, as well as constipation and hemorrhoids," as important focal infective factors in uroinfections. It is certain that, in infections of the urinary organs and passages caused by the colon bacillus group, a large percentage of these organisms come from the intestinal tract. M. Solis-Cohen (3) presented evidence from the literature in support of this view. He directed attention to the preponderance of infection with colon bacilli; bacilluria among females during attacks of gastro-enteritis; the more frequent occurrence of right-sided lesions on the theory of direct lymphatic extension from the adjacent cecum; colon stasis of fecal current; damage to the large intestine as by constipation, and to colonic focal infection. Kretschmer (4) found that 30 per cent of his patients with renal infection of the colon bacillus type gave a history of constipation. Some of his patients suffered from inflammatory and suppurative disease of the colon and anorectum. He firmly believes that these lesions produce and perpetuate uroinfection.

Of great importance in these studies is the knowledge of Nissle's work, which established the fact that different strains of colon bacilli differ qualitatively and possess different antagonistic colon bacillus indexes. Utilizing Nissle's results, Peretz and his associates (5) studied seventeen cases of uroinfection caused by the colon bacillus group. In fifteen patients they found associated intestinal disease or dysfunction. In all instances a definite qualitative relationship between the colon bacilli recovered from the urine and the feces of the same patient was found. Peretz concluded that there exists a definite relationship between infection in the urinary tract and pathologic states in the intestinal canal, as well as between the types of colon bacillus present in the urinary tract and the colon. The therapeutic deductions are of course self-evident.

The recent study by Baehr, Schwartzman and Green-span (6) on *B. friedlander* infections is of vast importance. They showed that this organism is a common intestinal habitant, and that it may be recovered from suppurations due to the perforative lesions of the appendix and colon. Their views are supported by Dudgeon (7), who found *B. friedlander* in the feces of 5.5 per cent of his cases, but felt that "these organisms were most commonly found in association with

an abnormal condition of the intestinal tract such as diarrhea, colitis, and in the later stages of typhoid fever." Like other enteric organisms, *B. friedlander* may gain entry into the general circulation and be excreted by the kidneys. It is the contention of Baehr and his collaborators that in the presence of obstruction, the urinary passages and organs may become infected. However, no obstruction existed in six of their fifty cases of urinary tract involvement.

Another interesting study is that of Neter (8, 9, 10, 11) who reported three cases of uroinfection caused by the dysentery bacillus, two of which were carriers. Dietrich (12) recently reported four cases of pyuria caused by dysentery bacilli. It is believed that uroinfection may follow or accompany an attack of intestinal bacillary dysentery, or it may occur in patients who present neither a history nor clinical evidence of intestinal bacillary dysentery. Neter (13) also reported two cases of infection of the urinary tract due to *Shigella* alkalescence.

Stewart (14) reported a case of pyelitis of pregnancy due to the Flexner type of the dysentery bacillus. In his case the stool cultures were negative for the Flexner dysentery bacillus. Another recent case of pyelonephritis of pregnancy caused by dysentery bacilli was reported by Neter (9). In this instance the same organism was found in both the feces and the urine.

The foregoing studies suggest that infection in the urinary tract with *B. dysentery* and allied species, originates in the intestines, notwithstanding the fact that bacillary dysentery has been regarded as an essentially localized intestinal disease.

In the consideration of urinary tract infections, it is surprising to note how little significance has been attached in the past to the inflammatory and suppurative ano-recto-colonic lesions. The terminal portion of the colon is continuously bathed in bacteria coming from the upper respiratory and the upper digestive tracts. It has been established that many people possess preformed anal ducts which empty into the crypts, but lead to racemose multi-glandular structures situated in the perianal tissues (15). Embryologically, these anal ducts appear at the time the prostate and the paraurethral glands do and possess a histologic resemblance to them (16). These ducts are lined with a secreting columnar epithelium, which in the branches becomes cuboidal (16), and are believed to be natural incubators for bacteria. The invading organisms may spread into the surrounding tissues producing inflammatory and suppurative states of local and focal significance. Hirschman (17) and others (18), have called attention to the significance of the crypt infections as foci. These observations have been amply substantiated. Hemorrhoids, have as a rule been looked upon as innocent lesions, and have

rarely been thought of as foci of infection. However, Reiman (2), Kretschmer (4), and others, have recognized them as possible foci of infection. Malmgren's (19) pathologic studies of hemorrhoidal tissue removed at operations, showed some evidence of infection in all sections. Thrombosis was found by him almost constantly in all types of hemorrhoids. The fact that thrombosis is an expression of an inflammatory process has been greatly underrated.

It is of importance to report case histories of patients seen during the past nine years, which illustrate exemplary types of the pathologic processes discussed in the preceding dissertation, and which suggest effective treatment. It should be observed that not all symptoms and observations may, however, be found in any single case. The term fecal stasis, as used in this paper, denotes the evidence of feces in the colonic circuit, especially in the cecum and ascending colon, after the taking of 30 to 45 cc. of castor oil which is followed by two or more bowel evacuations. This evidence was elicited roentgenologically in the survey films of the abdomen which were taken on several different occasions. Many of the patients had had complete urologic studies as well as various forms of accepted urologic treatment without permanent beneficial effects. However, these patients responded well to therapy described in this paper, and have remained well.

Case 1. S. T., a physician, 26 years old, had had an attack of right renal colic with urinary frequency in April, 1929, when he required morphine. Several similar episodes occurred in the past which had always been relieved by enemata. The only other pertinent point in the history was constipation of long standing with occasional blood streaked stool. Physical examination was normal throughout except for spasm of the anal sphincter. Routine urinalysis showed a moderate number of leucocytes, colon bacilli, and streptococci. A survey roentgenogram of the abdomen showed evidence of stasis of fecal current in the cecum and ascending colon. No abnormalities in the urinary tract were observed. Immediate therapy consisted of castor oil catharsis and colonic irrigations. Subsequently, regular bowel habits were established with the aid of a proper diet and agar. During this regime there was a continuous diminution of the pathologic elements in the urine.

In April, 1937, following a period of anxiety, there was a recurrence of constipation. Right renal pain and pathologic elements in the urine followed. The immediate therapy consisted of colonic irrigations and castor oil catharsis. The response was prompt and dramatic. Since then constipation has been avoided with the aid of acidophilus milk and agar. An excretory urogram, done in November, 1937, was normal, as was the urine.

Case 2. A white man, 30 years old, was seen by a urologist in March, 1937, because of intermittent episodes of right renal colic, urinary frequency, and dysuria. Physical examination was normal. Urinalysis showed a trace of albumin, leucocytes, and colon bacilli. The survey film of the abdomen revealed evidence of stasis of fecal current after the administration of one ounce of castor oil, which was followed by two evacuations. Complete cystoscopic studies, including ureteral exploration with a wax tipped catheter, were normal. Periodic ureteral dilatations were of no avail. Distinct improvement was observed following castor oil catharsis and colonic irrigations, and has been maintained by the use of agar and an anti-constipation diet.

Case 3. Mrs. L. M., 36 years old, was seen in February, 1935, because of frequent episodes of pain in the right renal region and loin, constipation, nausea, and occasional

vomiting. Physical examination revealed poor nutrition, and tenderness and spasm of the sigmoid. Proctologic investigation showed a superficial posterior fissure, a deep crypt, hypertrophied papillae, and marked spasm of the anal sphincter. The urinalysis revealed a trace of albumin, numerous leucocytes, and colon bacilli. Survey films of the abdomen repeatedly showed evidence of stasis of fecal current. Gastro-intestinal roentgen ray films demonstrated evidence of retention of barium in the colon after seventy-two hours. Following palliative local treatment to the anal lesion, it was possible to resort to colonic irrigations and castor oil catharsis. Under this regime she improved rapidly and felt so well that she refused subsequent roentgen ray studies of the urinary tract. A urinalysis done in August, 1935, and in September, 1935, was normal.

These three cases illustrate a possible relationship of fecal stasis to the initiation and perpetuation of pyuria. Two of these cases also had anorectal disease of moderate degree. The good results that followed therapy directed to the colon alone are clear cut and definite. Cases number 1 and 3 have been followed up for a long time.

Case 4. Miss F. F., 22 years old, was seen in June, 1930, because of backache and constipation of long standing. Of more recent origin was a throbbing anal pain which was aggravated during defecation. Physical examination showed spasm of the ascending and descending colon, and two infected crypts of Morgagni accompanied by hypertrophied papillae. Routine urinalysis revealed numerous leucocytes and colon bacilli. After excision of the infected crypts and the hypertrophied papillae, a gradual disappearance of the pathologic elements of the urine was observed. After complete healing of the wound, and establishment of regular bowel habits, the urine gradually but spontaneously became normal. No recurrence was observed during a follow-up period of about eighteen months.

Case 5. Mrs. T. N., 30 years old, was seen in December, 1937, because of intermittent left renal colic, diuria, nycturia, and dysuria. Constipation of long standing and the habitual use of cathartics were the only pertinent points in the past history. Physical examination was normal throughout. Proctologic investigation showed a posterior anal ulcer with an infected deep crypt and a sentinel pile, as well as marked spasm of the anal sphincter. Urinalysis revealed numerous leucocytes, staphylococci, and colon bacilli. The survey film of the abdomen showed stasis of fecal current in the entire colon. The excretory urogram revealed a normal urinary tract. The anal lesion was easily excised. The convalescence was uneventful. With the aid of diet, agar, and acidophilus milk, regular bowel habits were established. After five months, the voided urine was found to be free from pathologic elements. She has remained well to date.

Case 6. Mr. J. K., 86 years old, was seen in March, 1938, because of sharp pain on defecation and total hematuria. The past history was irrelevant. Physical examination showed signs of advanced senility, poor nutrition, suprapubic tenderness, and prostatic enlargement. Proctologic investigation revealed a posterior ulcer, deep crypts of Morgagni, and spasm of the anal sphincter. Residual urine measured 190 cc. Urinalysis showed numerous erythrocytes, leucocytes, and albumin graded three pluses. Because of the age and general condition of the patient, a urologic study and anorectal operative interference were deemed inadvisable. The bladder was irrigated and the anal lesion treated palliatively. After three weeks the urine was grossly clear and the anal lesion was much improved. Subsequently, after the passage of a hard stool, there was an exacerbation of the anal lesion with a prompt recurrence of pyuria. The residual urine then measured 100 cc. Again with the clearing up of the anal lesion, definite improvement of the urinary picture ensued.

These three cases illustrate the possible relationship of anorectal inflammatory and suppurative lesions to urinary tract infection. These anorectal lesions were also responsible for sphincter muscle spasm with resulting constipation. Fecal stasis coexisted in case number 5 and was demonstrated roentgenologically. Roentgenograms were not done in the other two cases. The effects of the treatment directed to the anorectal lesions again speak for themselves.

Case 7. Mrs. G. B., 27 years old, was known to have had chronic ulcerative colitis of long standing with periodic relapses consisting of bloody diarrhea accompanied by urinary frequency and dysuria. Physical examination showed definite undernourishment, diffuse abdominal tenderness and spasm of the sigmoid, and percussion tenderness over both kidneys. The sigmoidoscopic and roentgen pictures were typical of advanced chronic ulcerative colitis. The urinalysis, during the periods of remission, showed an occasional leucocyte, and a few gram-positive cocci in the sediment. During relapses the urine is loaded with leucocytes, gram-positive cocci, and gram-negative rods.

Case 8. Mrs. A. S., 56 years old, was seen in May, 1938, because of bloody diarrhea. She had first observed diarrhea sixteen years ago, and a year later an appendicostomy had been performed which was kept open for one year. Periodically she develops bloody diarrhea which is associated with urinary frequency, tenesmus, and dysuria. The urinary and colonic symptoms usually subside simultaneously. Her past history includes a plastic vaginal operation, and a hemorrhoidectomy. Her son died of "colitis," and one daughter has chronic bacillary dysentery. Physical examination was normal throughout. Recto-sigmoidoscopic examination showed a uniformly reddened and easily bleeding mucous membrane. Examination of the stool revealed numerous leucocytes, erythrocytes, and streptococci. No dysentery organisms, amoeba, or cysts were found in the stool, mucosal scrapings, or crypts aspirations. The urinalysis showed a moderate number of leucocytes and a trace of albumin. The culture was sterile. During remission, the urine was free from leucocytes on two occasions. Her blood serum agglutinates Flexner dysentery antigens V and Z in 1:320 dilution.

Case 9. Miss G. M., 11 years old, developed "colitis" in March, 1925. Eight years later she developed left renal colic and spontaneously passed a small calculus. Cystoscopic studies were normal except for leucocytes with few clumps in the urine from the bladder and the left kidney. The cultures were sterile. The left pyelogram showed a normal kidney and ureter except for a constriction without obstruction at the level of the fifth vertebra. A culture of the bladder urine repeated on April 19, 1932, showed *B. coli* and short chained streptococci. Her blood serum agglutinates the Duval-Sonne antigen in dilution of 1:320.

In November, 1936, a permanent ileostomy with exclusion of the distal portion of the ileum was performed by Dr. Marino at the Brooklyn Hospital, because of a continued upgrade progress of the colonic disease, which was complicated by polyps of the colon, and polyarthritides. On several subsequent occasions the polyps were fulgurated uneventfully. Five or six days following the last fulguration which was done on April 3, 1938, she developed sharp pain in the left kidney and loin with an elevation of temperature which persisted for several days. Cystoscopic studies were done on April 25, 1938. The left pyelogram showed dilatation of the pelvis and the upper portion of the ureter. The bladder urine contained hyaline and a few granular casts, a moderate number of erythrocytes and a few leucocytes with rare clumps. The right kidney urine showed amorphous urates. The urine from the left kidney revealed many red blood cells, a moderate number

of leucocytes with small clumps, and a few granular casts. All cultures of the urine were sterile.

The foregoing three cases show the association of urinary tract infection with inflammatory states of the colon. Urinary frequency, dysuria, and pathologic elements in the urine accompanied each episode of diarrhea in cases number 7 and 8. The disappearance of the diarrhea and the urinary symptoms usually occurred simultaneously. Of special interest is the occurrence of fever, pain in the left kidney, and pathologic elements in the urine following fulguration of polyps in the defunctioned colon in the last case.

DISCUSSION

During the past nine years I have encountered thirty definite instances of uroinfection which were associated with intestinal disease or dysfunction. Fourteen of these cases were studied in detail. Additional cases are now under study. The urinalysis in each instance showed an acid reaction, leucocytes, either gram-negative rods, gram-positive cocci, or both, traces of albumin, and occasional erythrocytes. The urinary tracts were otherwise normal. This was corroborated in nine cases where complete urologic investigations were made. The survey films of the abdomen, taken in twelve instances, showed evidence of fecal stasis, usually in the cecum and ascending colon. In eleven patients proctologic disease was present. Crypt infection was found five times, anal ulcer four times, and pectinosis (contracted anus) twice.

Stasis of fecal current, most frequently of proctologic etiology, was the most common intestinal observation. In association with ano-recto-colonic disease, it presents a source of both local and focal infection. It is possible that fecal stasis, if of long duration, could damage the colon (20). The colon then may act as an important portal of entry for enteric organisms into the blood and lymph streams.

There is ample reason to believe that suppurative and inflammatory states about the anorectum (2, 4, 17, 18), with or without fecal stasis, have focal infective possibilities. Hence, proctologic lesions should be searched for and properly evaluated in all cases of uroinfection, especially in the acute and recurring types of pyelonephritis caused by the colon bacillus group. It is noteworthy that even those who contend that foci of infection play little or no role in chronic uroinfections, agree with Von Lichtenberg (21) and Winsbury-White (22), that infection of the prostate gland or uterine cervix does cause and perpetuate uroinfection. These genital infections or inflammatory states are frequently kept active by distant foci of infection which must be eradicated. In bacteriuria and in some cases of renal infection where superficial tissues are involved, the removal of foci of infection have at times been followed by spectacular recovery (23). In this connection, one should remember M. Solis-Cohen's (3) recommendation, "to make sure that the bacterial focus, as well as the diseased tissue, is removed, because so long as infecting germs are permitted to remain, a cure of the secondary infections they are producing cannot be expected."

The treatment in this series of cases consisted of colonic irrigations, castor oil catharsis, agar, acidophilus milk, anti-constipation diets, and the eradication of ano-recto-colonic inflammatory and suppurative disease. The subjective complaints, renal colic and pain, disappeared promptly. The disappearance

of the pathologic elements in the urine was gradual, but at times very slow, requiring several months. Treatment to the urinary tract was avoided except in case number six, but even in this instance, the influence of the anal lesion upon the pyuria was clear cut.

The uroinfections encountered in my patients appear to have been of the moderate and subacute recurring types. Whether or not they have any relationship to the chronic forms has not yet been determined. On general principles, I feel that these infections should be eradicated promptly and permanently as a matter of prophylaxis against recurrence and chronicity. Special attention to derangements and disease of the intestinal tract, and to other foci of infection, if present, should be given in all cases of uoinfection, if only on an empirical basis. For the past quarter of a century, Beer (24) routinely administered castor oil to his patients suffering from uoinfections, with the idea of bringing about complete evacuation of the colon. Beer (25) found this simple therapy very effective in many cases of renal infection. I had the rare opportunity to observe and study his material. I feel that where castor oil therapy is ineffective, the colobacilluria should be considered of secondary etiologic significance, as this therapy acts almost as a

therapeutic test. Kietzschmer (4) also long ago recognized the etiologic relationship of stasis of fecal current and of the inflammatory and suppurative lesions of the anorectum to uoinfections. He noted that the eradication of the intestinal lesions, or the correction of the existing colonic dysfunction materially hastened the eradication of the kidney infections. Bugbee (26) too, stressed the influence of stasis of fecal current on the various forms of pyelonephritis.

SUMMARY AND CONCLUSIONS

1. Stasis of fecal current and inflammatory and suppurative disease of the ano-recto-colonic tube, are capable of producing and perpetuating uoinfections. Cases of urinary tract infection caused by the colon bacillus group should especially have a careful intestinal survey for evidence of the aforementioned ano-colonic lesions or dysfunction.

2. These uoinfections usually disappear following the eradication of the intestinal lesions. They are not primary urologic problems. Illustrative case histories are presented.

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Our Present Knowledge of the Action and Sources of Copper in Nutritional Anemia

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THE clinical picture of the use of copper and iron in haemoglobin formation as at present described, has been variously stated. These statements conflict to such an extent that a review seems timely. While there seems to be a wide difference of opinion among a few, there is the possibility of neglected factors that will reconcile all of them.

Most medical men were taught and the literature states that the formation of haemoglobin depended

upon the presence of iron. They are also taught that massive doses (two to six gms.) are more effective than doses which approached the utilization level of the organism (15 to 50 mgm.). In all cases, large doses of iron were more effective than small doses. But iron is not the whole answer. (All physiological reactions are due to the presence of either an enzyme, hormone, vitamin or catalyst or other determiner). Though three-fourths or more of the "massive dose" was known to be excreted, yet results in haemoglobin

formation were better. The answer to this remained unknown until the work of Hart, directing the investigation of a group of workers at the University of Wisconsin, showed that iron will not correct anemia, whereas iron in the presence of another factor would do so. It was necessary therefore to break down the composite ash used and determine the action of each ingredient. For no single mineral element is capable of carrying on the function of an animal tissue in the absence of a balanced proportion of "trace" minerals.

The same group of workers (1) demonstrated that inorganic iron, when accompanied by traces of copper can be used as the only source of iron for the cure of anemia in rats. It has been shown that manganese (2, 4) and amino acids (3) are completely inactive when purified and cannot replace copper in the utilization of iron. Chickens, mice, pigs and cattle exhibit the same haemoglobin response shown by rats. Since that time many carefully controlled experiments with infants and adults have been carried out, showing the specificity of copper as the catalytic agent in haemoglobin formation. If copper acted only as an accelerating catalyst, its adoption would be indicated. However, there have appeared statements to the contrary with some variations and it would be well to review these and see whether the difference is one of kind or degree.

The supplementary value of copper with iron therapy has proven itself in many instances. Results from giving 75 grs. (Blaud's) daily were far from encouraging except when 1.5 mgms. of copper sulphate were added (5). Where other means of treatment have failed, copper will prove to be a valuable adjunct (6). In nutritional and secondary anemia iron and copper in combination was more effective than iron alone (7). Iron is best utilized in the presence of copper, which is necessary for haemoglobin synthesis (8). Nearly all workers agree that copper is an active agent in haemoglobin synthesis (9). Copper does not increase iron retention, but does increase its storage in the liver (10). Copper did not influence iron retention. The effect of the copper was to increase the proportion of retained iron found as haemoglobin (11). The presence of copper is necessary for the utilization of this stored iron (in liver) in the production of haemoglobin (12). Maximum response to iron therapy is often lacking until copper is added (13). Patients taking iron and copper showed a gradual improvement in both red cell count and haemoglobin levels (14). Patients taking reduced iron showed a gradual reduction in both red cells and haemoglobin. Diet alone does not seem to furnish a sufficient amount of these basic elements. In some cases the cure of nutritional anemia will not take place unless an adequate amount of copper is given (15). The average haemoglobin values were 15% higher (Iron and Copper) than controls (iron alone) (16). A combination of iron plus copper and Vitamin B produced the optimum increase in the haemoglobin content (17). "Iron and ammonium citrate with copper sulphate is usually all the treatment needed in a pure nutritional anemia. Even in a severe case it is exceptional that one is unable to bring the haemoglobin to normal in four or five weeks by this treatment. We lay stress on the time element because we do not think it is a good thing for a young child to remain anemic any longer than necessary during the period of rapid

growth. I have never understood the interest of some of my friends in methods of treatment which take months to manifest their effects" (18). "Iron alone usually stimulates a slight increase in the formation of haemoglobin . . . but the response is inadequate. Iron supplemented with copper causes a maximum response in the regeneration of haemoglobin" (19). We now come to realize that this capacity (the maintenance of a normal haemoglobin concentration) depends on other factors besides the quantity of iron supplied—for instance the simultaneous supply of copper and other elements (20).

The foregoing references clearly indicate the function of copper in body metabolism. "The presence of copper can no longer be regarded as accidental . . . the metal, though present only in traces has a distinct function in which it cannot be replaced by any other element" (21). Of the several functions undoubtedly exercised by copper in the body, only one is known with any certainty—its essential role in the formation of haemoglobin.

In a recently published book (22) two statements are of importance in this regard. "Its (copper) chief value to human health is its effect on the availability of iron as a cure of anemia." "A trace of iron in the milk is not sufficient but a trace of copper in addition to the iron will cure anemia." (In test animal).

A second group agree that copper plays this important catalytic role, but believe that medicinal iron contains a sufficient amount. "Copper appears as a natural contaminant in practically all iron preparations in amounts sufficient to bring about the desired results" (23). If this statement is true, and copper is necessary, then it leaves more to a chance therapy than is usual in treatment. The analysis of 10 iron preparations (24) showed two contained no copper and others a trace that was insignificant (.0083 mgm. to .0443 mgm. per gram). The spectroscopic examination of 65 medicinal iron preparations (25) showed a mere trace or complete absence in 44 or 68%, and in only 11 (17%) did copper occur to the extent of .005%. This is about 1/100 of the minimum requirement if a gram a day of these iron preparations were used. Ferrous gluconate was used in hypochromic anemia (26) with good results. But ferrous gluconate is reported heavily contaminated with copper. The authors make no reference to this factor. When iron was administered in large doses the effect of copper was negligible (27). This last statement is a confirmation of the work previously reported in 1931 (28). There is little doubt but that the iron preparation was contaminated with copper. The larger dose increased the amount of copper intake. Large doses of iron recommended by some (29) seem uncalled for. The additional iron is excreted and valueless except as it gave up its copper content. No mention is made of copper (30) but it is stated . . . "27 to 36 grains of iron ammonium citrate is obviously not an adequate dose." Too liberal an amount of iron may cause a phosphorus deficiency since the excess iron would give the insoluble phosphate. Animal experiments have repeatedly shown that excess iron interferes with phosphorus retention.

There is a third group that admit this important role assigned to copper, but believe it to be present in foods to such an extent that medicinal copper is unnecessary. This might more easily be true of iron, calcium or iodine, to name a few of the food factors

that have of necessity become pharmaceutical products. But no matter. We must examine their point to see if it is at all necessary for copper to join this group. "In experimental animals iron can be absorbed and stored in the liver, but cannot be converted into haemoglobin unless copper is also present. In man, deficiency of copper is extremely rare" (31). "The optimal dose of copper is so small that extreme precautions must be taken to exclude it from the food and iron in order to demonstrate its effects. The artificial addition of copper to ordinary foods or iron preparations therefore is superfluous, and such administration of copper in anemia appears irrational" (32). The foregoing statement seems irrational since iodine and some of the vitamins are required in smaller amounts than copper. These have an established place in therapy. Vitamin C has a wide distribution in nature. It was thought no one could be deficient except in a very restricted diet. Yet a Vitamin C intake below minimum is frequently noted. Iron deficiency is apparently quite common, yet it is present freely in nature. "Accessory elements are supplied in sufficient quantities by almost any diet" (33). If this were true of copper it would necessarily be true of iron. The human organism does not utilize its entire intake of iron. Copper deficiency is one of the reasons. Copper is much more easily left out of the diet than iron.

A recent review gives the iron and copper content of over one hundred and fifty foods in common use (34). This review is as accurate as it is possible to secure due to differences in source of supply. From the iron and copper content of these foods, even allowing for 50% utilization of copper, and an average of 50% utilization of iron, we would conclude that copper deficiency would be more frequent than iron deficiency. Yet we find the following statement appearing: "It is not necessary to add copper to the preparation of iron—ordinary diet contains sufficient amounts of that element" (35). "Copper is necessary in nutritional anemia, but it was present in milk and foods to such an extent that it was unnecessary as a therapy" (36).

One of the listed causes of anemia was a deficiency of copper (37). (The author had a question mark after "copper"). "Milk in receptacles of copper or alloys of copper results in an increased copper content of milk to the amount present in human milk. A little copper is present in some other foods. In the presence of anemia recovery may be hastened by the addition of small amounts of copper for short periods of time" (38).

Here we have a partial answer to the present day difference of opinion regarding copper—"Milk in receptacles of copper." Every milkman knows milk absorbs copper and he has guarded against too great an absorption by tinning the copper receptacles. (Above one part per million of copper in milk tends to give an "off" flavor). This absorption by milk from copper equipment has frequently been the source of copper for test animals supposedly on a "copper free" diet. Just as copper has to a great extent departed from our kitchen, so it has for some years been on the way out in our milk processing plants, both fresh and evaporated. This last source of copper was not in existence previous to pasteurization and is disappearing so rapidly that its absence is definitely noted and its restoration must be secured through some other avenue. That is what has happened in other deficiencies and this nutritional deficiency follows much the

same course as others. That haemoglobin can be raised to a high level without added copper (39) may mean that the milk used was processed in copper equipment. The processing plants of fruit and vegetables are keeping copper out of contact with the food far more than previously as equipment and processing changes are made. These changes to stainless steel and vacuum cooking are definitely advantageous to the industry and to people, but to say that one can continue to depend on them for either a minimum requirement of copper or even a stated amount, is unwarranted. "Five per cent of nutritional anemias are due to copper deficiency" (40). If that were true in 1934, it is many times higher than that now and is still on the increase, due to equipment changes in the entire food processing field.

Copper is present in certain vegetables, fruits and animal foods. But here the source is as variable as the soil. In the last analysis it is the soil that yields the mineral food elements for plants and through plants to animals. Complete mineral fertilization of the soil is not the primary objective of the food producers, and depletion of one or more factors takes place frequently without their knowledge. The optimal requirement of copper is so small that it is easily left out of the diet and the soil, under present conditions. Foods, ultimately from the soil, may easily contain less than the minimum requirements. About one hundred crops will deplete the soil of "trace" elements unless they are restored. This "non-medical" factor is of importance to the clinician. The statement that, "when iron compounds alone fail (to increase haemoglobin) then give iron and copper," is based on the supposition that the diet may contain enough copper. It will, if the dietary intake of copper containing foods is increased beyond caloric requirement.

Tradition need not necessarily continue to govern a therapy after the reason for its continuance no longer survives, especially when a change can be of distinct advantage. The variation in the copper content of medicinal iron even to its complete absence is far too great to retain or secure the confidence of the clinician.

Many infants and children can and do live on a level of 9 to 10 gm. of haemoglobin per 100 cc. But would a higher level of even 12 to 14 gm. be better? There can only be one answer. And that same answer is true for the adult as well as for the child. If 14.5 gm. or 15.4 gm. of haemoglobin per 100 cc. of blood is normal, then whatever food or therapy (or both) is necessary to bring it to that level should be used. Another approach to this problem of whether massive doses of iron (far beyond body requirements) or small doses of iron with "measured" amounts of copper is given in Buerger's theory (41). From this theory it is concluded that small doses of combined substances will produce a better effect than large doses of individual substances.

The problem of too much copper in food has been a cause of concern in the past. This problem is no longer one of importance, due to the industrial changes previously mentioned. Further than this, comparatively large doses of copper showed no pathology (42). Copper does not show toxic effects in the test animal until a level of 150 times its therapeutic dose is reached.

The iron storage depots in the body have immense capacity. This is necessary since iron does not fall in the category of substances freely absorbed by the

gastro-intestinal tract. The only "trace" elements stored in the liver or the foetus are copper and iron and this storage reaches its peak at birth (43). Nature makes this effort to store "copper" with iron and not manganese or cobalt. Manganese seems essential for the production of the secretion of the Anterior Pituitary, (catalyst). (Without manganese there is no haemoglobin disturbance, but the above secretion is decreased in amount). Storage of iron to any extent would hardly occur in nutritional anemia if iron alone were responsible for the deficiency. Nor would there be iron storage in iron deficiency. Another factor is deficient, and the iron in storage awaits this factor, copper, before it can be utilized. The copper present in the tissues of the organism can hardly be available except in malnutrition. Copper must be present in the iron storage depots if the iron is to be utilized for haemoglobin formation. The liver, as the most important of these storage depots, stores both. Its copper content is responsible, in part, for its action in anemias.

A few points need to be emphasized in copper-iron

therapy. It is best given with food. On an empty stomach there is nausea and sometimes emesis. Given with food three times daily in recommended dosage there is a rapid rise in haemoglobin content. This rapid rise causes an increase in appetite. If this appetite is in any way satisfied, there will frequently occur a corresponding increase in weight. This increase in weight may or may not be desirable to the patient or to the physician.

SUMMARY

1. The evidence is submitted from a number of reliable sources that copper is necessary and a specific catalytic agent in haemoglobin formation.
2. The amount of copper present as a contaminant of therapeutic iron is entirely a matter of chance.
3. Copper is present in some foods but in wider variation than iron. In food absorption through processing this source of copper has almost completely been eliminated.
4. In nutritional anemia it is important to be certain of the presence of copper.

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An Experimental Study of the Rhythmic Contractions in the Small Intestine of the Dog

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THE problem of the caudad progress of food residues is one which has aroused much investigation by physiologists. The demonstration by Bayliss and Starling of the myenteric reflex in the small intestine of the dog seemed to offer a reasonable explanation for the caudad direction of the peristaltic wave. They demonstrated that this reflex is mediated by the intrinsic enteric plexuses.

Alvarez (3) was unable to demonstrate the myen-

teric reflex constantly in the small intestine of the rabbit or cat. He noted, however, that different parts of the small intestine in the rabbit show variations in respect to rhythmicity. Thus, the jejunum was found to contract rhythmically at a greater rate than the ileum, the upper part of the jejunum showing a rate of about fifteen contractions per minute. So constant was this finding that he suggested the term "gradient of rhythmicity," indicating that it is a property of jejunal muscle to contract and relax rhythmically at a higher rate than ileal muscle.

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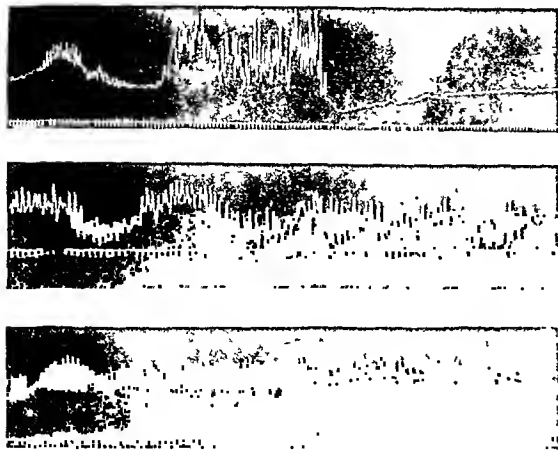


Fig. 1. Types of intestinal movement in exteriorized loop of small bowel of dog. Upper tracing—peristaltic wave. Middle tracing—irregular segmentation with tonus waves. Lowest tracing—rhythmic contractions.

This finding was confirmed in the dog by Puestow, using isolated segments of small intestine, and by Castleton, using exteriorized loops of small intestine in continuity. The latter further noted that variations in the nature of the diet do not affect the rate of rhythmic contractions per minute, although Cannon (7) has pointed out that carbohydrate food passes more rapidly through the small bowel of the cat than does protein or fat food.

Alvarez, Hosoi, Overgard and Ascanio made a study of the effects of section of extrinsic nerves on the small bowel of the rabbit. It was found that after vagal and splanchnic section the rate of rhythmic contractions per minute was constantly less, in both the jejunum and the ileum, than in the normal animal. This indicated that, in the rabbit, the extrinsic nerves play some part in the maintenance of the normal rate of contraction of the musculature of the small bowel. In view of the fact that there is still dissent as to the function of the extrinsic nerves of the alimentary canal with respect to intestinal activity, it was decided to study the effect of section of these nerves on the rhythmic contractions of the small bowel of the dog.

METHOD

Because of the emphasis which has been laid by physiologists on the importance of the intrinsic enteric nervous mechanism, it was thought that the use of loops of bowel in continuity rather than isolated segments was preferable in the present study.

Accordingly, exteriorized loops, in continuity, enclosed in bipedicle tubes of skin, were prepared at various levels of the small bowel of dogs (6). These loops have the mesenteric blood and nerve supply intact to a large extent, since in their preparation it is only necessary to split the mesentery at an avascular region between two mesenteric vessels. The operation is a simple one but, since a tube of skin from the abdomen about 2 inches wide is required, it is advisable to use females.

When the skin around the exteriorized bowel is well healed, it is possible to observe the activity of the loop with a reasonable degree of accuracy. The activity was recorded by a double-tambour air-displacement

system, the receiving tambour being attached to the loop by an aluminum clip. The animals were trained to lie quietly on the observation table for three-hour periods. Daily records of intestinal activity were taken under various conditions of fasting and feeding and during sleep, and the occurrence of rhythmic contractions was noted.

The observations were repeated after section of the vagus and splanchnic nerves. Vagotomy was performed by a thoracic approach through the ninth interspace on the right side. The nerves were sectioned as they lie on either side of the esophagus immediately above the esophageal hiatus in the diaphragm. At this situation they have united after leaving the pulmonary plexus but have not yet divided into the various rami which supply the abdominal viscera. Splanchnicotomy was performed by a two-stage lumbar route. No mortality occurred after the nerve sections and the animals appeared to be as strong and healthy as before.

RESULTS

It soon became apparent that rhythmic contractions were a relatively rare type of activity in the preparation used. As seen in the loop they corresponded very closely to the classic description given by Cannon (8) for this type of activity in the small bowel of the cat, contiguous segments relaxing and contracting with the greatest regularity. More common was another type of segmentation, progressive in character, a number of segments contracting in a serial fashion from above downward. Most common of all, however, was a completely irregular type of segmentation, segments contracting in a complex way, which defied analysis. Both the progressive and the completely irregular types of segmentation gave very irregular tracings characterized by changes in amplitude and rate (Fig. 1—middle tracing). The rhythmic contractions, on the other hand, gave characteristic tracings, which were regular as to both amplitude and rate (Fig. 1—lower tracing). In 9,900 minutes of tracing they occurred for only 232 minutes, or 2.3 per cent of the tracings counted.

The normal animal. One hundred and seventy-eight observations of rhythmic contractions were made over a period of three months in the normal animals. The number of rhythmic contractions per minute in these observations was relatively constant for each segment of bowel. Variations from day to day were noted. Thus in dog 4 (Table I), in which the loop was prepared in the middle part of the ileum, the average number of rhythmic contractions per minute in twenty-five observations over a six-week period was 13.4. However, on two occasions, rates of fourteen contractions per minute were noted in eight observations, while on other occasions rates of twelve contractions per minute occurred in two observations. Slight variations from day to day of this order were seen in all the animals.

Observations were made on the fasting and on the recently fed animal. The number of rhythmic contractions per minute was the same in each of these physiologic states. However, it was observed that the occurrence of rhythmic contractions was less common in the bowel of the recently fed animal than in that of the fasting animal. The bowel of the former showed continuous activity, the commonest types of movement being the progressive and the irregular types of segmentation and the peristaltic wave. Great varia-

TABLE I

Rate of rhythmic contractions in dog 4 before and after section of extrinsic nerves

Date	Average Number of Rhythmic Contractions Per Minute	Number of Readings	Minimum and Maximum
February 4	13.7	6	12-14
10	14.0	4	14
23	12.7	5	12-13
24	13.0	3	13
March 3	13.3	3	13-14
14	14.0	4	14
March 16	Left splanchnicotomy		
21	12.5	3	12-13
22	12.8	5	12-14
23	13.5	4	13-14
24	12.8	9	12-14
April 11	Right splanchnicotomy		
12	12.7	5	12-14
21	12.3	6	12-13
25	13.8	5	12-14
28	12.4	10	12-13
May 2	Bilateral thoracic vagotomy		
16	13.0	4	13
24	12.6	6	12-13
25	13.4	7	13-14
26	13.1	10	13-14
27	13.0	6	12-14
31	12.5	2	12-13
Total number of readings			107
Number of contractions per minute			
Average before nerve section			13.4
Average after left splanchnicotomy			12.9
Average after right splanchnicotomy			12.8
Average after vagotomy			12.9
Minimum and maximum			12-14

tions in tonus and amplitude were seen in all these types in the digestive state. The bowel of the fasting animal, on the contrary, showed long periods of quiescence alternating with periods of activity. It was at the end of one of these periods of activity in the fasting animal that rhythmic contractions were most commonly observed.

The animals frequently slept during the observation period and it was possible to observe rhythmic contractions during sleep. Periods of rhythmic contractions did not occur any more commonly in the sleeping animal than in the animal when awake. The rate of rhythmic contractions per minute was the same when the animal was asleep as when it was awake, and the general activity of the bowel was unaffected.

The rate of rhythmic contractions per minute in each of the loops was found to be related to its level in the small bowel (Table II). Dog 1, in which an exteriorized loop was present in the upper part of the jejunum, showed a rate of about eighteen contractions per minute. Dog 5, in which a loop was present in the lower part of the ileum, showed a rate of about twelve contractions per minute. The other animals, in which loops were present at various intermediate levels, showed corresponding rates of contraction per minute. In other words, the higher the loop in the small bowel,

the higher was the rate of rhythmic contractions per minute.

Observations after splanchnic and vagal section. A total of 280 observations of rhythmic contractions were made after left splanchnicotomy, after right splanchnicotomy and finally after double vagotomy. As far as could be determined from tracings of intestinal activity and from observations of appetite and bowel habits, the small bowel did not show any disability from the loss of these nerves. Dog 3 showed diarrhea for a few days after the second splanchnicotomy, a finding which has been noted in man after bilateral splanchnicotomy for hypertension.

The rate of rhythmic contractions per minute was noted to be unaffected by the nerve sections. Thus in dog 2 the average rate of rhythmic contractions was about fourteen per minute. After splanchnic section and after vagal section the rate was still about fourteen contractions per minute (Table III).

A similar series of observations were made in the other animals, with substantially the same findings (Table II and Fig. 2).

A detailed description of each of the series of observations would simply involve repetition and for this reason the details of observations on dogs 2 and 4 only have been presented in tabular form. The other animals showed comparable results.

COMMENT

The fact that the rate of rhythmic contractions in the small bowel is a constant for any given segment has been recorded by Alvarez (1, 2), Puestow and Castleton. That this is true in the Magnus preparation as well as in the intact animal is also well-known. But as pointed out by Alvarez and his associates (4), in the rabbit the rate in a Magnus preparation is constantly about 25 per cent less than in vivo. The reason for this decrease in rate is by no means clear, although Alvarez and his associates found

TABLE II

Gradient in rate of rhythmic contractions in the small bowel of the dog

Dog	Site of Loop	Average Number of Rhythmic Contractions Per Minute		
		Before Splanchnicotomy	After Splanchnicotomy	After Vagotomy
1	Jejunum 6 in. below ligament of Treitz	18.0	--	17.9
2	Ileum 30 in. above cecum	13.9	13.8	13.8
3	Ileum 23 in. above cecum	13.8	13.8	13.8
4	Ileum 10 in. above cecum	13.4	12.8	12.9
5	Ileum 4 in. above cecum	12.5	12.4	--
Total number of readings		158		
Observation period		6 months		
Variations		+1		

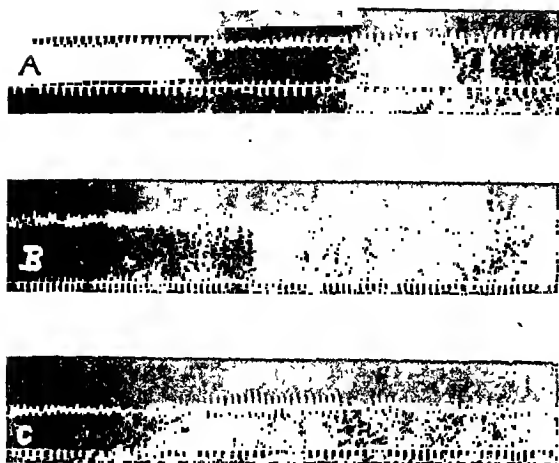


Fig. 2. A. Rhythmic contractions in small bowel of dog before and after section of extrinsic nerves. B. After bilateral thoracic vagotomy. C. After bilateral splanchnicotomy. The rate is the same before and after section of extrinsic nerves.

a considerable decrease in rate after extrinsic nerve section.

Thomas and Kuntz have shown that in dogs which have been given sufficient doses of nicotine to paralyze the synapses in the intrinsic intestinal plexuses and hence to arrest all types of movements which depend on the integrity of the plexuses, rhythmic contractions proceed actively with the greatest regularity and constancy and, moreover, at the same rate as before nicotization. They concluded that the rate of rhythmic contractions is probably a function of intestinal musculature, while the variations in amplitude and tonus noted in the normal bowel are a function of the nervous control of the intestine in response to environmental changes.

The fact that the rate of rhythmic intestinal contraction in the dog is not affected by section of extrinsic nerves is additional evidence of the autonomy of the intrinsic intestinal mechanism as far as rhythmic contractions are concerned. The fact that the same does not hold in the rabbit may be evidence of the less highly developed state of the small bowel of the latter compared with that of the dog. Johnson has noted histologic changes in the myenteric plexus of the dog's bowel after degenerative extrinsic nerve section.

The fact that fasting or feeding had no effect on the rhythmic contractions except that they were less commonly observed in the active bowel of the recently fed animal is of interest. The great activity in the latter is accompanied by great changes in tonus and amplitude and it is possible that these are expressions of the nervous activity elicited in response to the functions of trituration and transport. In the empty bowel of the fasting animal, however, fewer demands are made on nervous co-ordination and it is possible that the more common occurrence of the rhythmic contractions, constant in amplitude and rate, is the expression of muscular activity less affected by nervous control.

Castleton reported that, if the mesenteric nerves supplying an exteriorized loop of bowel in the dog were sectioned, there was no change in the rate of rhythmic contractions but that, if the whole mesentery with its blood vessels were sectioned and the loop completely isolated, deriving its blood supply from the skin of the loop, the rate decreased by about 25 per cent. This is in harmony with the findings of Puestow, who reported, in the dog, in loops completely isolated in the abdominal wall, rates of rhythmic contractions which were constantly 25 per cent slower than those noted for analogous loops in the present study.

Whatever factor is responsible for this decrease in rate, it is evidently not the extrinsic nerves of the bowel.

SUMMARY

Exteriorized loops were prepared at various levels in the small bowel of trained dogs and the occurrence and rate of rhythmic contractions noted.

Rhythmic contractions were found to be a relatively rare form of movement in these preparations, occurring in about 2 per cent of all tracings. The remain-

TABLE III

Rate of rhythmic contractions in dog 2 before and after section of extrinsic nerves

Date	Average Number of Rhythmic Contractions Per Minute	Number of Readings	Minimum and Maximum
January 20	13.8	5	13-15
February 14	14.0	5	13-15
24	13.7	3	13-15
March 1	13.8	4	13-14
2	14.1	5	13-15
March 3	Left splanchnicotomy		
14	13.7	14	13-14
19	13.7	4	13-14
20	14.2	5	13-15
March 22	Right splanchnicotomy		
23	14.0	2	14
24	13.4	4	13-14
April 11	13.6	3	13-14
12	13.6	4	13-14
13	13.6	16	13-14
14	14.0	6	13-15
April 21	Double thoracic vagotomy		
25	14.1	6	13-15
26	14.8	6	13-15
29	13.8	6	13-15
May 5	13.8	4	13-14
7	13.6	5	13-14
18	13.4	5	13-14
23	13.2	7	13-14
Total number of readings			118
Number of contractions per minute			
Average before nerve section			13.9
Average after left splanchnicotomy			13.5
Average after right splanchnicotomy			13.8
Average after vagotomy			13.8
Minimum and maximum			13-15

ing 98 per cent of the tracings was occupied by irregular types of segmentation, peristaltic and tonus waves.

The rate of rhythmic contractions was a constant for any given loop with a variation of plus or minus one contraction per minute.

The rate of any given loop was found to be a function of its distance from the pylorus, the loop at

the highest level having the highest rate, that at the lowest level having the lowest rate.

The rate was not affected by fasting, feeding or sleep, except that in the recently fed animal, rhythmic contractions were less commonly observed than in the fasting animal.

The rate was unaffected by degenerative vagal and splanchnic section.

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An Experimental Study of Some Chemical Inhibitors of Gastric Acidity

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INVESTIGATIONS on the experimentally produced peptic ulcerations have definitely proved that chemical and mechanical factors are of major importance in the production of these lesions and in prevention of their healing. A logical approach to the treatment of peptic ulcer would be to decrease the acidity or amount of gastric content to which the lesion is exposed. As a matter of fact, most of the clinical methods of treatment of peptic ulcer have had one or both of these objectives. In a series of investigations, one of which is herein reported, we have attempted to determine if there are substances or groups of substances which will inhibit the secretion of a gastric mucosa when the latter is subjected to a definite stimulus. In this paper we are reporting the effects on gastric acidity observed immediately after administration of several substances followed by the administration of histamine.

In 1938, Atkinson and Ivy (1) reported the results of a study of the effects of a varied series of substances on gastric acidity in the dog. These authors sought to produce prolonged effects by means of frequent and continued treatments. They found that none of the substances studied would bring about an enduring achlorhydria without also producing toxic effects.

METHOD

Dogs which were either trained for gastric analysis or provided with Heidenhain pouches were used. Solutions of the reagents studied were placed in the empty stomach or pouch and withdrawn after a specified time. Immediately after this treatment 1 mg.

of histamine (ergamine acid phosphate), was injected subcutaneously and fractional gastric analysis was made. The stomach or pouch was emptied at fifteen minute intervals until secretion had practically ceased. Free and total acidity were determined by titration using Töpfer's reagent and phenolphthalein as indicators. Secretion during the period of treatment was found to interfere with the action of the agent studied; hence observations were made only when the stomach or pouch was initially inactive.

EXPERIMENTAL RESULTS

The substances principally studied were: mercuric, cupric, lead, manganese, and zinc salts; hydrogen peroxide, quinone, hydroquinone, and resorcinol; and the dyes, brilliant green and crystal violet. These will be discussed in the order named.

The highest acidity attained following histamine stimulation was used as a criterion of ability to produce acid. As is well established, this should normally be quite constant in a trained dog or a Heidenhain pouch. Control gastric analyses were done following any procedure which caused a reduction in gastric acidity. Additional controls were afforded by experiments in which the procedure had no effect on gastric acidity. Except as will be later noted, the effects observed were quite transitory, acidity being normal on the day following an experiment in which it was markedly affected. Since the control values did not vary greatly either on one dog or between different animals, it was reasonable to assume that in the absence of treatment the gastric acidity would at least attain a fairly definite minimal normal value. For the experiments reported, this value was about 120 clinical

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units for the dogs with Heidenhain pouches and about 95 clinical units for the dogs with intact stomach.

It was found that dilute solutions of cupric acetate or nitrate (0.0005 M.) and mercuric chloride (0.00025 M.) effected a reduction in gastric acidity, while lead acetate or nitrate (0.01 M.) concentration had no

TABLE I

Effect of heavy metals on the secretion of the intact stomach: Highest free acidity, in clinical units, after 25 cc. of the specified reagent has been allowed to act for two minutes

Dog	Substance	Acid
A	0.1% Cu (NO ₃) ₂	5
B	0.1% Cu (NO ₃) ₂	8
A	0.1% Pb (C ₂ H ₃ O ₂) ₂	100
B	0.1% Pb (C ₂ H ₃ O ₂) ₂	103
A	0.1% MnCl ₂	95
B	0.1% MnCl ₂	108

effect (Tables I and II). In the experiments reported the treatment was so adjusted that acidity was markedly reduced but complete achlorhydria was not produced. Thus an approximate measure may be had of the relative concentrations of cupric or mercuric salts necessary to produce an effect when a constant volume of solution is allowed to act for a constant time. In an intact stomach the factors of volume and time of action cannot be held very constant; consequently, much quantitative variation in effect was observed, although it was qualitatively constant. Quantitative variations were also noted in the effect of the same treatment on different pouches, possibly because the pouches were of different sizes. Complete temporary achlorhydria could also be produced in either the intact stomach or the pouch by increasing the concentration of the effective agent or the time of action.

Culmer, Atkinson and Ivy (2) (1937) have shown that repeated gastric lavage with 3 per cent solution of hydrogen peroxide causes prolonged achlorhydria in dogs. Irritation and bleeding are also caused by this procedure. Much more dilute solutions of hydrogen peroxide (0.05 M.) were studied. As stated by Culmer and his co-workers, the effect of dilute solutions of hydrogen peroxide on gastric acidity appears to be quite variable, although an effect is definitely present. Relatively small reductions of acidity appeared to be associated with extensive catalytic decomposition of hydrogen peroxide.

Quinone in 0.01 per cent solution was found to cause marked reduction in acidity, while no effect was noted for 1 per cent resorcinol or 1 per cent hydroquinone (Table 3). None of these solutions were apparently very irritating or toxic. One-tenth per cent quinone completely prevented acid secretion, and marked reduction persisted twenty-four hours after the treatment. This procedure brought about a slight bleeding from the pouch, which began about an hour after exposure of the pouch to quinone and continued in one dog for three days and in another for six days. In the former case the fasting mucous secretion was just

perceptibly colored, while in the latter a definite brownish tinge was produced. Appetite and general behavior of the dogs were not affected.

One per cent solution of brilliant green and a saturated solution of crystal violet (somewhat less than 1 per cent) completely prevented acid secretion when first administered; the following day acidity was greatly reduced (Table IV). A bleeding reaction was produced, similar to that caused by quinone. In this case the bleeding did not begin until two days following the treatment and in one dog was slight, while in another a considerable quantity of dark brown fluid was produced, the dog being otherwise apparently unaffected. Following treatment with the dyes the pouches were washed repeatedly until practically all excess dye was removed. The day following the procedure the gastric juice was colored, the color deepening in successive samples. One-tenth per cent solution of brilliant green caused reduction in gastric acidity when administered but no persistent staining of the mucosa, enduring effect on gastric secretion, or bleeding. One per cent solution of Congo red showed no tendency to stain the mucosa or to affect gastric secretion.

TABLE II

Effect of heavy metals on the secretion of the Heidenhain pouch: Highest free acidity, in clinical units, and total volume of secretion, in cc., after 10 cc. of the specified reagent has been allowed to act for ten minutes

Dog	Substance	Acid	Volume
C	0.001 M. Cu (C ₂ H ₃ O ₂) ₂	10	7.0
E	0.001 M. Cu (C ₂ H ₃ O ₂) ₂	10	9.0
E	0.0005 M. Cu (C ₂ H ₃ O ₂) ₂	90	9.5
E	0.0005 M. Cu (C ₂ H ₃ O ₂) ₂	95	12.5
D	0.0005 M. Cu (NO ₃) ₂	76	8.5
E	0.0005 M. HgCl ₂	3	7.5
E	0.00025 M. HgCl ₂	28	10.0
E	0.00025 M. HgCl ₂	33	7.5
F	0.00025 M. HgCl ₂	8	7.5
D	0.00025 M. HgCl ₂	16	7.5
E	0.005 M. Pb (C ₂ H ₃ O ₂) ₂	125	12.5
D	0.01 M. Pb (NO ₃) ₂	120	9.0
E	0.01 M. MnCl ₂	139	10.0
E	0.1 M. ZnSO ₄	125	12.5

The volume of the secretion was not as constant as the maximum acidity in these experiments, although quite constant volume is attainable. No clear-cut changes in volume were noted, so the total amount of acid produced varied about as the maximum acidity. When achlorhydria was produced, the gastric juice was usually more or less mucoid, although the volume

might be considerable. However, the acidity could be reduced to as low as 15 to 20 clinical units with the juice remaining water-clear and not becoming perceptibly mucoid or viscid.

Nearly normal acidity was observed two to three hours following marked reduction in acid secretion, so probably an inhibition initially not complete is

TABLE III

Effect of quinone, resorcinol and hydroquinone on the secretion of the Heidenhain pouch: Highest free acidity, in clinical units, and total secretion volume, in cc., after 10 cc. of specified reagent has been allowed to act for ten minutes

Dog	Substance	Acid	Volume
G	0.01% quinone	66	6.0
G	0.01% quinone	59	6.5
V	0.01% quinone	49	7.5
G	0.02% quinone	16	7.0
F	0.1% quinone	0	9.0
F	Twenty-four hours after above treatment	56	6.5
H	0.1% quinone	0	17.0
H	Twenty-four hours after above treatment	47	14.0
G	1% resorcinol	118	4.0
F	1% resorcinol	122	11.0
F	1% hydroquinone	108	10.5
I	1% hydroquinone	132	10.0

about gone by that time. However, except in the case of the dyes, there is no reason to believe that the active agent has any tendency to remain in the mucosa. Whenever a prolonged reduction of acidity was produced, bleeding also followed, although there did not appear to be any severe toxic effect. Just how much inhibition can be produced without causing bleeding has not as yet been determined.

COMMENT

The effects observed appear to exhibit a certain specificity. This seems hardly to be accounted for by the general toxicities of the substances studied. The evidence is not sufficient for any definite conclusions, but the reasons why such specificity was expected will be outlined.

It was suggested by Mathews (3) (1920) that the gastric hydrochloric acid is formed by the hydrolysis of ammonium chloride with subsequent absorption and removal of the ammonia. Rigoni (4) (1930) and Martin (5) (1932) proposed that the ammonium ion necessary for this mechanism is produced from urea by the gastric urease. Martin suggesting a process somewhat different from the original hypothesis of Mathews.

If the gastric urease is essential for the production of hydrochloric acid, one would expect substances which inactivate urease to inhibit acid production. Luck and Seth (6), who in 1924 originally described

gastric urease, found that it has the same enzymotic properties as soy bean urease. Thus it may be pertinent to consider studies on the inactivation of soy or jack bean urease.

Hellerman, Perkins and Clark (7) (1933) have shown that crystalline urease may be inactivated by oxidation of its sulphydryl groups, which is readily effected by copper or mercury. This process does not involve denaturation of urease protein and can be reversed by reducing agents such as hydrogen cyanide or hydrogen sulfide. Schmidt (8) (1928) found that silver, mercury and copper are the three most effective of a large number of metals in the inactivation of extract of jack bean urease, mercury being two to three times as effective as copper. One would not expect silver to act on the gastric mucosa because of the great insolubility of silver chloride. Lead, manganese and zinc are relatively ineffective. Quastel (9) (1933) reported that hydrogen peroxide and a number of polyhydric phenols are powerful inhibitors of urease. Hydroquinone was one of the most effective phenols; quinone was about twice as effective as hydroquinone. However, Quastel has presented evidence that the inactivation is not due to the phenols directly but is brought about by quinones formed from them; resorcinol, which does not form a quinone, having no inhibiting action. The lack of effect of hydroquinone on gastric acidity may thus be in accord with the evidence of Quastel. Quastel (10) (1932) has also found that the basic triphenylmethane dyes, including crystal violet and brilliant green, are powerful inhibitors of urease. This inhibition does not appear to take place by the same mechanism as inactivation by copper or mercury.

TABLE IV

Effect of dyes on the secretion of the Heidenhain pouch: Highest free acidity, in clinical units, and total secretion volume, in cc., after 10 cc. of specified reagent has been allowed to act for ten minutes. Acidity noted immediately and after a specified time

Dog	Substance	Time, Hours	Acid	Volume
E	Sat. crystal violet	22	18	12.5
		52	89	17.0
F	Sat. crystal violet	Immediately	0	5.5
		24	12	9.5
F	1% brilliant green	Immediately	0	11.5
		18	2	14.5
		42	66	7.5
I	0.1% brilliant green	Immediately	52	8.0
F	1% Congo red	Immediately	125	11.5

Thus the effects observed on gastric acidity may be explained on the basis of a temporary inactivation of the gastric urease. It should be pointed out, however, that although urease appears to be especially sensitive, other enzymes may be inactivated by oxidation of sulphydryl groups (11); other endocellular enzymes might be involved, although there is no especial reason

for supposing that they are. It is recognized that the explanation presented is by no means the only one possible and it is hoped that further study will secure more evidence.

SUMMARY

Transitory achlorhydria to histamine may be produced in dogs by exposure of the gastric mucosa to

dilute solutions of mercuric or cupric salts; no effect was noted using salts of lead, manganese and zinc in much greater concentration. Quinone has a similar inhibiting action, while hydroquinone and resorcinol have no effect in 100 times as great concentration. Brilliant green and crystal violet stain the gastric mucosa and inhibit acid secretion.

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A New Effective Parasiticide in Giardiasis

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UPON appraising the clinical aspects of giardiasis and reviewing the persisting controversy regarding giardial pathogenicity, a student of the subject is seized with great temerity if he contemplates any study or observations in this field. Since Stiles' brilliant studies on the lamblia intestinalis or giardia in 1915, the clinical proving grounds of giardial pathogenicity have developed into a scientific quicksand in which research into the problem has been promptly swallowed and almost as promptly forgotten. Each year sees a goodly number of publications see-sawing back and forth as to whether lamblia intestinalis can cause symptoms or not. The growing significance of the problem is appreciated when one reviews the results of investigations into the incidence of giardial infestation as the years go by.

During the past few decades there have been constant and repeated attempts to find a satisfactory, effective parasiticide for giardial infestation by gastroenterologists and those dealing with parasitic infestation. There have been at least 50 various parasitocides used in the attempt to kill the parasites. Among these parasitocides are numbered stovarsol, carbarsone, acetarsone, neoarsphenamin, aldarson, arspenamin, mercurochrome (dimol), hexamethylenamin, silver nitrate, salol, santonin, emetin, ipecac, thymol, beta-naphthol, calomel, methyl blue, Chaparro amargoso, and numerous other drugs, all hopelessly employed by various observers. These parasitocides have uniformly been characterized by failure—both on laboratory and clinical grounds. It is not within the province of this paper to enter into the controversy as to whether giardia are pathogenic or not. This paper is presented as a preliminary report to (a) de-

scribe our experiences with a new parasiticide atabrine, whose use against giardia has not been reported in the American or English literature; (b) to stimulate the use of this parasiticide by other clinicians; (c) to evaluate by this comparison other experiences with what appears to be a most effective giardial parasiticide.

During a review of the foreign literature, the authors came upon the report by Galli-Valerio, Professor of Parasitology at Lausanne, Switzerland, who reported remarkable success with atabrine as a giardial parasiticide. He found that 51 out of 54 cases of giardiasis were cured by atabrine. This observation was subsequently uniformly corroborated by 12 other continental investigators, over periods of observation running up to two years. Our results reported below are in agreement with these observations, which stimulated our trial of the drug. It is reasonable to believe that once an effective giardial parasiticide is available, a more satisfactory method of determining the question of giardial pathogenicity will be available. However, from the experience of the essayists, it may not be amiss to express an opinion here regarding this problem.

A review of some of the studies made on a large scale may serve to recall the high incidence of giardial infestation in the general population, when special preparations are made of the stool specimens and studied by trained investigators. Stiles examined 1287 school children of Washington, D. C., and found 13% of 672 boys infected and 8% of 615 girls.

Of 2300 soldiers serving overseas (1917) Kofoid and his co-workers found 5.7% infected. Of 576 soldiers on home service, 22% were found infected.

Jepps in 1921 found 13.2% of 971 English soldiers infected and Mathews and Smith in 1919 found 16.4%

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of 4068 English soldiers convalescent from dysentery infection.

Mileny, Bishop and Leathers found 14.7% of 20,237 individuals infected.

Faust and Heudler in 1936 found 16.6% infection among 4270 ambulatory clinic patients at Tulane University in New Orleans.

It is thus apparent from these figures that the giardia is easily the most common intestinal flagellate inhabiting the human intestine. It is also obvious from the above that any claims for pathogenicity of the giardial organism should be regarded with greatest caution and with a healthy skepticism. It is probably true that frequently giardia is a secondary invader in diarrheas or gastro-intestinal diseases of a primary non-giardial cause.

On the other hand local inflammatory and catarrhal inflammation in the small intestine may well occur—which is usually asymptomatic but may cause some derangement in the digestive processes. This seems entirely a reasonable assumption when one considers the vast numbers of giardia that occur in the infested individual. Chandler and Porter have estimated the number of cysts in a single stool to exceed 14,000,000,000. The number of cysts in the average stool in the case of only moderate infection, to occur in the vicinity of over 300,000,000. One should consider at this point the fact that these parasites are equipped with a sucking disc occupying three-quarters of the ventral surface, and it is by this sucking disc that the parasite clings to the intestinal mucosa and sets up mechanical irritation.

Schindler was the first to note that almost every giardia patient into whose stomach he looked—through the gastro-copie—had a gastritis. In collaboration with Dr. Chevalier L. Jackson, the authors have made the same observation. In our experience with the biliary drainages in patients infested with giardia, a duodenitis is usually found from the duodenal aspirations as indicated by a marked increase in duodenal cell exfoliation, or a plus two or more positive occult blood reaction. The local silent enteritis may be analogous to the silent early gastric carcinomas, peptic ulcer, and gastritis which can occur without any clinical symptoms manifesting themselves, until some precipitating factor as infection, dietary, nutritional or hygienic abuses, etc., may break through the barrier of the intestinal mucosal resistance and cause more pronounced physiologic functional and organic disturbances in the digestive process.

This is in accord with the pathological studies made by H. E. Robertson at the Mayo Clinic. This observer found that on careful studies of the gastro-duodenal mucosa in a large group of specimens, especially prepared, that between 10 and 15% of these patients had evidence of gastro-duodenal ulceration at some time during life. These patients had never noted any symptoms that led to any suspicion of a peptic ulceration. These figures were corroborated by Eusterman and Balfour in their treatise "Diseases of the Stomach and Duodenum."

In the words of William Beaumont, "It is interesting to observe to what extent the stomach may become diseased, without manifesting any external symptoms of such disease, or any evident signs of functional aberration. Extensive active or chronic disease may exist in the membranous tissues of the stomach more

frequently than has been generally believed." This profound observation has been corroborated by many other gastroscopists as well as by the authors in our gastroscopic studies. The same observation undoubtedly applies to the small intestinal mucosa which is inflamed by the vast numbers of attached giardia. It is then possible that the giardia may become pathogenic under certain circumstances which may lower the protective barrier of the mucosa and institute physiologic changes sufficient to produce clinical symptoms.

We present a comparatively small group of patients in the nature of a preliminary report, but a considerably larger group has been tested and found to be just as satisfactory. However these have been omitted for purposes of scientific appraisal since they did not conform to our requirements for frequent biliary drainages to search for the parasites, patients did not remain under observation for adequate periods of time, or were uncooperative, etc. Hence we have limited the study to 10 very carefully and intensively studied cases.

The drug atabrine has the chemical name, dihydrochloride of methoxylchloroethyl aminopentyl amino-acridine. Atabrine is a derivative of alcyamino-acridine and discovered by Mietzsch and Mauss in 1931 at Elberfeld, Germany. Hecht in testing its pharmacological qualities found that in the animal it was rapidly absorbed from the digestive tract impregnating the blood in a strong concentration, but greatest in the biliary system. In the sacrificed animals, following the administration of the drug, the superior portion of the small intestine was strongly colored and coated with the yellow drug. Even after several days following an injection, subcutaneously, the duodenum and the small intestine are very rich in atabrine. The lower portion of the small bowel and the colon are not anywhere nearly as affected. The drug is reabsorbed in the small intestine and takes part in the cycle known as the entero-hepatic "circulation of the bile salts." The drug is known in Europe as Quinacrine.

In 1932 Green and Hoops independently reported for the first time, the superiority of atabrine over quinine in the cure and prevention of malaria.

We have used approximately the same average dosage as is employed in malaria, i.e. one and a half grains three times daily taken orally for five days. An interval of one week should then elapse before a similar dose is again administered, if necessary. In this way any possibility of a toxic reaction is avoided, although we have not encountered any toxic symptoms in any of our cases. The treatment is thus most simple and comparatively inexpensive.

From the accompanying tables it is seen that atabrine was a completely successful parasiticide in nine out of ten cases of giardiasis. It is also noted that the eradication of the parasiticide caused complete abolition of symptoms in some cases, moderate improvement in others, and no improvement in certain others. This observation may also represent the pathogenicity of the parasiticide in each instance, and it may not. However, speaking from the clinical phase it should be stated that when one has used other attempted parasiticides in giardiasis and compares the results with the effect of atabrine in the clinical picture, we gain the impression that despite the

absence of "control" studies, atabrine is definitely helpful clinically in some of the cases. In those cases where the giardia is a secondary invader, it is obvious that symptoms persist as long as the fundamental cause persists, despite the eradication of the parasites.

The foreign authors are unanimous in not finding any recurrences up to two years, following the use of atabrine. This has been our experience with the drug to date.

SUMMARY

1. This paper is presented as a preliminary report

to stimulate interest in a new parasiticide, so that its usefulness may be thoroughly evaluated.

2. Atabrine is the most effective parasiticide available in the treatment of giardial infestation.

3. On an average treatment of one year, 9 out of 10 cases of giardiasis have remained free of any recurrence of the parasite, giving a 90% efficacy in a small but carefully controlled group of giardia infested patients.

4. The treatment is extremely simple, inexpensive and apparently non-toxic.

Due to lack of space the tables are not published

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Diastase Activity of Blood and Urine when the Pancreatic Ducts are Permanently Closed*

By

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AS early as 1908 Schlesinger (1) demonstrated that the activity of the diastase in the blood of rabbits was notably increased by ligating the duct of Wirsung. On the third day the diastase value was 5 to 10 times the normal. Thereafter it quickly dropped to its former level. He states that Grutzner found that the diastase ferments of the urine were likewise increased by tying the main pancreatic duct in rabbits. Since then a number of investigators have found that ligation of the main pancreatic ducts in dogs or rabbits always causes a marked increase in the concentration of the blood diastase. (Clerc and Loeper (2), Wohlgemuth (3), Gould and Carlson (4), King (5), Elman and McCaughan (6), deTakáts and Nathanson (7), Johnson and Wies (8)).

In 1917 McClure and Pratt (9) reported an experiment in which double ligatures were placed around the pancreas of a dog at the junction of the processus lienalis and the corpus, and at the junction of the processus uncinatus and the corpus. The diastase activity of the urine increased from 1 unit the day prior to this procedure to 200 units two days later.

They also obtained a rise to 50 units in one experiment and 100 units in another when small pieces of the pancreas were imbedded in the spleen. The increase in these three instances only persisted from one to four days. deTakáts and Nathanson (7) later demonstrated by a similar experiment which consisted of placing ligatures about the entire pancreas near the junction of the corpus pancreatis and the processus lienalis that a rise in the concentration of diastase in the blood occurred when, as in the experiment of McClure and Pratt, the ducts in only a portion of the gland were obstructed.

All observers have concluded that after tying the pancreatic ducts the concentration of blood diastase after an initial rise falls to normal within a few weeks and usually within the first ten days. Gould and Carlson (4) observed a pronounced secondary rise about the third and fourth week, and in two dogs there was a third rise about the fifth week. They stated "that the length of time required to return toward the normal after the secondary rise is usually much greater in the dogs in which total ligation had been performed than in the case of those in which the two ducts only are ligated and in three cases out of four

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even at the end of two months and a half the diastatic power of the serum still remained considerably above the normal." Gould and Carlson as well as the other investigators who studied blood diastase values after tying "both" pancreatic ducts failed to demonstrate that they had permanently excluded all the pancreatic secretion from the duodenum. To occlude all the ducts permanently is a difficult procedure as the pancreatic juice usually destroys the tissue about the ligatures and re-enters the intestine. Furthermore there are frequently more than two ducts in the dog as Hess (10) has shown.

From the time of Claude Bernard many attempts were made to exclude all the pancreatic juice from the intestine with little or no success. Lombroso (11), Fleckseder (12) and others claimed that they had occluded all the pancreatic ducts and in spite of the supposed absence of pancreatic digestion the animals did not lose weight and the digestion of fat and nitrogen was essentially normal. At autopsy the pancreas was not notably reduced in size. Thanks to the operative skill of F. T. Murphy in the first studies from our laboratory by Pratt, Lamson and Marks (13) it was clearly demonstrated that when all the pancreatic juice was excluded from the intestines the dogs lost weight rapidly and passed large fatty stools. Chemical studies showed that 50 to 90 per cent of the fat and 50 per cent or more of the nitrogen in the food fed was not absorbed. The pancreas underwent a rapid atrophy and within two or three months was converted into a small dense mass consisting chiefly of fibrous tissue.

The present study deals with the changes in the activity of blood and urinary diastase of dogs in which permanent occlusion of all the pancreatic ducts was accomplished. Diastase values in blood and urine are of clinical importance because the increase in them that occurs in acute pancreatic necrosis has often proved an aid in diagnosis.

MATERIAL AND METHODS

The findings reported in this paper are based on observations made on twelve dogs in which the pancreas was separated from the duodenum. Determinations of diastase activity in the blood was continued for many months on the animals that survived.

The operations were performed by Dr. Lester R. Whitaker, and owing to his surgical ability the occlusion of all the pancreatic ducts was complete and lasting except in one dog. At a second operation on this animal he succeeded in permanently excluding all pancreatic juice from the intestine.

Operations were performed under ether anesthesia on dogs which had been given 0.065 gram of morphine sulphate about an hour previously. The portion of the pancreas attached to the duodenum, the corpus pancreatis (Pflüger), was dissected free from the intestine. All connecting strands between these two structures were cut except one or two blood vessels which were left to provide adequate blood supply for the duodenum. The pancreatic ducts and any threads of tissue indistinguishable from small ducts were cut between double ligatures. When the dissection was complete the border of the body of the pancreas could be drawn away one to two centimeters from the duodenal wall. Between the duodenum and the freed body of the pancreas a portion of the omentum was interposed and held in place by fastening it with stitches

to the surrounding structures. This procedure of separating the pancreas and duodenum by a barrier of omental tissue was devised by F. T. Murphy with the object of preventing the formation of sinuses between pancreas and duodenum.

For determining the diastase activity of blood and urine the improved method of Wohlgemuth (14) was used. In this a solution consisting of 0.1% soluble starch (Kahlbaum)* and a buffer phosphate mixture (pH 7.2) in 1% sodium chloride is employed. Into each of a series of 12 small test tubes 1 cc. of a 1% sodium chloride solution is pipetted. Various dilutions of the blood serum, the amount decreasing by arithmetical progression, are placed in this series of test tubes beginning with 1 cc. in the first two tubes and then 2 cc. of the buffered starch solution added to each. The tubes are kept at 38° C. for thirty minutes. After cooling rapidly, a few drops of N/50 iodine solution are added to each tube. The partly digested starch assumes a purple color, the completely digested starch a light yellow color. The end point is in the last tube that shows a purplish hue. The next lower dilution of serum yields a pure blue color. Let us suppose the end point is reached in the fourth tube. The diastase activity which was able to begin the digestion of starch in the dilution of serum present in this tube is calculated as follows: Diastase units = $2^4 = 16 \frac{(38^\circ)}{(30^\circ)}$. The units expressing the diastatic value are the number of cubic centimeters of 1% starch solution which will be converted into erythrodestrin by 1 cc. of blood serum. With this technique values between 4 and 64 are normal.

This method has been used with satisfaction both in this country and in Europe. Although not accurate it is entirely satisfactory in measuring the wide variations in diastase activity found in our study. It has also been extensively employed in the diagnosis of acute pancreatic necrosis in German clinics.

DIASTATIC ACTIVITY OF THE BLOOD

The value of blood diastase in the ten normal dogs examined ranged from 8 to 64 units, with an average of 32. This confirms the observations of deTakáts and Nathanson (7) using the same technic who found the concentration of diastase fairly constant, varying from 32 to 64 units. The highest normal value observed in the blood of a dog was 80 units. (Wohlgemuth and Noguchi (15)).

Within twenty-four hours after separating the pancreas from the duodenum there was a great increase in the activity of the blood diastase amounting to 800 per cent in the dog showing the smallest rise, in which from the preoperative level of 64 units it rose to 512 units, and in the dog with the greatest increase in twenty-four hours, from 32 units to 2048 units.

The smallest maximum rise after shutting off all the pancreatic juice from the intestine in a series of twelve dogs was from a normal of 32 units to 512 units. This occurred at the end of forty-eight hours. The highest value of diastase obtained was 8192 units. This great concentration was present in the blood of two dogs. In Dog V this high level was found on the second day, and in Dog III on the fourteenth day after the closure of the pancreatic ducts. Usually the maximum rise took place on the second or third day.

*Wohlgemuth suggests that unsatisfactory results obtained with this method may have been due to failure to use Kahlbaum's preparation of soluble starch.

The operation of separating the pancreas from the duodenum often results in the development of acute pancreatic necrosis which is frequently of such severity as to cause the death of the dog. The question arises: Is the amount of blood diastase increased by the destruction of large amounts of pancreatic tissue in addition to that caused by occlusion of the pancreatic ducts? Our findings indicate that it is not. If comparison be made of the values obtained in rapidly fatal pancreatic necrosis with those observed in the blood of dogs in which occlusion of the pancreatic ducts produced no clinical evidence of pancreatic necrosis it is clear that the destruction of pancreatic tissue does not increase the diastatic power of the blood above that produced by occluding all the ducts. Dog I died on the seventh postoperative day. The blood diastase contained 256 units twenty-four hours after the operation and the maximum level of 1024 was attained on the third day. There were extensive fat necroses throughout the omentum and over the intestines. The pancreas was a necrotic mass. Dog II died on the second day after the operation of a fulminating hemorrhagic pancreatic necrosis. The blood at the end of twenty-four hours contained 2048 units. Dog X died on the third post-operative day. The blood diastase at the end of forty-eight hours measured 2048 units. At autopsy widespread areas of fat necroses were present throughout the abdomen. Dogs XI and XII made a good recovery although the content of blood diastase in each was also 2048 units on the second day. Still more conclusive is the observation on Dog V. This dog presented no clinical evidence of pancreatic necrosis and seemed well a few days after the operation, yet its blood contained 8192 diastase units on the second post-operative day. This was the highest concentration of diastase we have ever observed.

In the past it has been the accepted view that shutting off the pancreatic juice by tying the ducts causes only a transitory rise in the activity of the diastase of the blood usually lasting not over a week or ten days. From an examination of the published protocols it is evident that the attempt to exclude all the pancreatic juice permanently has rarely been accomplished. The typical signs of total pancreatic obstruction have not been noticed and the pancreas at autopsy with a few exceptions has not been greatly atrophied.

In a series of five dogs deTakáts and Nathanson (7) ligated in addition to the tail the "head" of the pancreas (corpus pancreatis) with a double silk ligature. This left a small portion of the pancreas about 2 cm. in diameter surrounding the main duct still secreting into the duodenum. The diastase values rose as high as 3072 units in three of the five dogs. Within two weeks following ligation of the gland the blood diastase values returned to normal. The explanation suggested, namely that this fall in diastase concentration is due to cessation of secretion on the part of the acinar cells in the ligated portion, cannot be accepted in view of the continued high diastase activity we have observed for a long period after all the ducts are closed. The increase of diastase values reported by deTakáts and Nathanson was as great as that occurring in most of our dogs. This shows that partial occlusion of the flow of external secretion may produce as great a rise as total exclusion, and is additional evidence that the pancreatic necrosis produced in our dogs in addition to the occlusion of the ducts

was not an important factor in the increase in blood diastase concentration.

The conclusion that when the flow of pancreatic juice into the duodenum is reestablished the blood diastase soon returns to normal is supported by many observations recorded in the literature. In three out of four of our dogs kept under observation many months with the pancreatic juice permanently shut off from the intestine the activity of the blood diastase continued elevated. The blood of Dog III contained 2048 units as late as the 46th day after operation and 256 units on the 97th day. In Dog IV, 1024 units of blood diastase were present on the 48th day, and 256 units on the 895th day. The blood of Dog VII after a second operation contained 512 units on the 325th day, and 128 units on the 551st day. In spite of the high blood diastase values present in Dogs IV and VII a year or more after the permanent exclusion of the pancreatic juice, nothing that could be definitely recognized as pancreatic tissue was found at autopsy on gross examination. The autopsy on Dog IV was made by Prof. H. E. MacMahon. His protocol reads in part as follows: "The main pancreatic duct can be traced into the duodenum and it admits a probe for a distance of 1 cm. and then probe meets some obstruction. Multiple sections through the mass of what appears fat and scar tissue lying in the inner curvature of the duodenum reveal nothing that one can say with certainty was pancreatic tissue. There are lumina which admit a probe. There are scars. There is fat tissue and here and there are smaller areas of softening. * * * At about 3 cm. from the duodenum one can pick up a pink cord-like mass of tissue 4 cm. in length which dwindles off rather indefinitely into connective tissue and fat tissue in the region of the spleen. The connective tissue covering this radiates out in all directions suggesting that at one time this structure had been much larger. * * * No duct could be traced or seen in the fibrous cord of pancreatic tissue described above."

On microscopic examination Prof. MacMahon found "little insular tissue highly vascularized, with an abundance of sympathetic nerve tissue. No ducts, no acinar tissue. Microscopic Diagnosis: Obstructive sclerosis of pancreas, with retention of islet tissue."

There would seem to be no doubt that the great diastatic activity which the blood exhibits within twenty-four hours after occluding the pancreatic ducts originates in the pancreas and is due to the passage of ferment from the cells of the pancreas into the lymph and blood. Wohlgemuth and Noguchi (15) showed that an increase of the activity of diastase in the blood could be demonstrated a few hours after the pancreas of the dog was traumatized. In one instance in two hours the diastase value had risen to 125 units and to 200 units in five hours. In another dog it had risen to 100 units in five hours.

That the increased activity of diastase in the blood of dogs in which the pancreas is completely atrophied cannot have its origin in the pancreas seems equally clear. Yet the atrophied remains of the pancreas would seem to play a role in maintaining the high value of blood diastase as the activity of blood diastase in depancreatized dogs is not abnormally high and is usually normal or less than normal according to the literature. The pancreatic remains of Dog VIII were removed nine months after occlusion of the pancreatic

ducts. The diastatic value of the blood was 64 units on the second day after the pancreatectomy and also on the fourth day. The dog died on the sixth day. A similar procedure was carried out on Dog XII 130 days after the pancreas was separated from the duodenum. At operation the atrophy was so complete that no recognizable pancreatic tissue could be found. The urine was free from sugar. The mass of fat and connective tissue at the site of the pancreas was carefully dissected out from the surrounding tissues and excised. The tissue on microscopic examination was found by Prof. MacMahon to be the remains of the pancreas "showing one small island of functioning acinar tissue, many small distorted groups of cells suggesting islets of Langerhans, an abundance of nerves, and ganglia, and areas of chronic and acute inflammation—most often associated with old sutures. Some vessels show regressive changes." The animal developed glycosuria within twenty-four hours. The blood diastase the first day after the removal of all pancreatic tissue was 64 units.

That the scar-like mass which occupied the site of the pancreas, in each of these dogs, although it bore no resemblance in appearance to the pancreas macroscopically and little microscopically, did contain functioning pancreatic tissue was proved by the development of diabetes when it was excised. If this small shrunken mass of tissue could influence carbohydrate metabolism it would seem probable that it influenced also the diastase content of the blood.

In only two of the dogs did the blood diastase fall to the preoperative level during the period of observation. In Dog VIII diastase was found in the same amount as before operation on the 86th day, but the fall to this point may have taken place any time between the 23rd and the 86th day as no determinations were made during this interval. The concentration of diastase in the blood of this dog, however, dropped to the maximum normal value, namely 64 units, as early as the 14th day. All the other dogs on which observations were made had a larger amount at this time. The other dog in which the diastase fell to normal, Dog VII had only 32 units on the 90th day compared to 64 units before operation.

There was evidence that the pancreatic juice was again entering the intestine of Dog VII. The stools were not bulky, nor did they contain an excess of fat and nitrogen, and the animal was not losing weight on the usual diet. At operation although no sinus from pancreas to duodenum could be recognized the pancreas was little, if at all, reduced in size although it was somewhat indurated. Observations on many dogs in our laboratory during the past thirty years have shown that when all the pancreatic juice is excluded from the intestine there is progressive atrophy of the pancreas until only a small sheet or cord of tissue remains measuring only a few millimeters in width or thickness and only a few centimeters in length or the atrophy may be even more marked with the result that no pancreatic tissue is recognizable macroscopically. At the second operation on Dog VII the pancreas was again carefully dissected from the duodenum and omental tissue interposed for a second time. This time the pancreatic juice was permanently excluded from the bowels and clinical signs of pancreatic insufficiency

persisted. The blood diastase rose to 1024 units on the 20th post-operative day and was 128 units on the 551st day. This was four times the pre-operative level. The animal had developed diabetes. *At autopsy no pancreatic tissue could be recognized.*

In this dog after the pancreatic juice reentered the intestine the blood diastase fell to normal. When the pancreatic secretion had been permanently excluded from the intestine the blood diastase amounted to 512 units nearly a year after the operation, and was 128 units after eighteen months. It would seem logical to conclude from this clear-cut experiment that when the pancreatic juice reenters the intestine the blood diastase drops in time to normal. When, on the other hand, the obstruction to the outflow of pancreatic secretion persists the blood diastase may remain elevated for at least eighteen months as this case shows. That the permanent obstruction of pancreatic secretion leads to a persistently high value of blood diastase cannot be accepted without modification as the studies on Dog VIII show. In this dog the blood diastase fell to normal by the 14th day and did not rise subsequently to a higher level. There was clinical evidence of complete lack of pancreatic digestion, namely, bulky fatty stools containing many muscle fibers when on a meat diet and loss of weight in spite of an abundant diet. Clinical studies showed that only 61.9% of the fat of the food, 50.9% of the nitrogen and 78.3% of the carbohydrates were absorbed, compared with 94.8% fat, 91.5% nitrogen and 98.9% carbohydrates prior to occlusion of the pancreatic ducts. At autopsy nine months after the exclusion of pancreatic juice the pancreas was reduced to a thin cord, 1 cm. wide at its widest portion, which was the remains of the corpus pancreatis. A short distance from this it was much narrower (3 mm.). The total length was 4 cm. Dr. MacMahon who made the microscopic examination reported that he was unable to find any recognizable acinar tissue. He says, "There is an abundance of islet tissue and a great abundance of sympathetic nerve ganglia and nerve cell fibers. The histological appearance would suggest duct obstruction of months duration." In view of the fact that the three other dogs with histological changes in the pancreas similar to those present in this dog had high blood diastase values we are unable to account for the normal diastase values found in the blood of this animal.

As many experimenters have demonstrated that the blood diastase increases after tying the pancreatic ducts but quickly drops to normal in dogs in which the pancreatic juice is not permanently excluded from the intestine, it would seem apparent that the persistent elevation in the concentration of the blood diastase in our dogs is associated in some way with the atrophy of the pancreas or the failure of any pancreatic juice to enter the intestine. That the high activity of the blood diastase maintained for many months in our dogs with atrophied pancreas can be attributed to the passage into the blood of pancreatic secretion retained in occluded ducts is untenable because the pathological examination of the pancreas remains revealed neither ducts nor secreting acini.

A sustained increase in the activity of the blood diastase in dogs has been observed by Cope, Hag-

stromer and Blatt (16) following hypophysectomy. In no other pathological state has a persistent elevation of the blood diastase been reported prior to the publication of the present paper.

DIASTATIC ACTIVITY OF THE URINE

The urinary diastase was determined before operation in five dogs. In the urine of one there were two diastase units, in that of the other four dogs no diastase activity was present. The first day after occlusion of the pancreatic ducts some diastase was found in the urine of all dogs examined but the concentration was slight. It was 8 units in three and 64 in two. During the first week after the operation the urine of eight dogs was examined and all specimens contained some diastase. The greatest values were found on the second or third day except in the case of Dog III in which the greatest activity was present on the fifth day. A single day's urine from two of the dogs contained 1024 units. In that of the other six dogs the diastase values never exceeded 64 units. There was no relation between the concentration of diastase in the blood and in the urine. For example, in the blood of Dog I twenty-four hours after blocking the flow of pancreatic juice were 256 units and in the urine 8 units. The blood of Dog II contained 2048 units after the same interval. Although there was eight times as much activity of the diastase in the blood of the second dog as in that of the first, that in the urine was the same in both animals. The blood of Dog I contained 1024 diastase units on the third day and the urine the same number. Two days later the diastase in the urine had dropped to 128 units although the concentration in the blood was unchanged. On the fifth post-operative day the blood of Dog III contained 2048 units and the urine 1024 units. On the 14th day the blood diastase of this dog had risen to 8196 units but the urinary diastase had fallen to 8 units. Although the blood of Dog IV contained a large amount of diastase between the 12th and 48th days the urine examined four times during this period had at no time more than four units. On the 48th day the

blood diastase was 1024 units and the urine was free from diastase.

From this study it is evident that closure of the pancreatic ducts results in the development of a small diastase value in the urine but the concentration bears no relation to that of the blood. After the first fortnight although the blood diastase remains at a high level the urine is usually free from diastase. None of these dogs had nephritis.

It would be a mistake to conclude from these observations on dogs that a similar lack of relation between blood and urinary diastase exists in man. The opinion generally held seems correct that when the diastase rises in the blood it is rapidly excreted into the urine by the normal human kidney. In acute pancreatic necrosis the diastase present in the urine often exceeds that in the blood. In fact the determination of the urinary diastase in this disease is more valuable for diagnosis than that of the blood diastase.

CONCLUSIONS

1. The permanent separation of the pancreas from the duodenum with the resulting permanent occlusion of all the pancreatic ducts in the dog resulted in a persistent increase of the activity of the diastase in the blood in three out of four animals. In one dog there was twice the maximum normal activity on the 551st day and in another dog there was four times, or 256 units, on the 895th day.

2. In spite of the increased value of diastase in the blood of these dogs the pancreas at autopsy was found reduced to a small mass in which few acinar cells could be demonstrated.

3. The source of the increased blood diastase in these dogs is unknown.

4. There was no relation between the activity of diastase in the blood and in the urine. There was a small number of diastase units regularly present in the urine during the first week after the occlusion of the pancreatic ducts but after the second week the urine was usually free from diastase although the blood continued to yield a large number of units.

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Studies in Human Biliary Physiology*

III. The Effect of Bile and Vitamin K on Experimentally Produced Hemorrhagic Diathesis in a Human With a Total External Biliary Fistula

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FOR many years, investigators in the field of physiology of the liver and biliary system have been aware of a hemorrhagic diathesis observed in jaundice and in biliary fistulae. Surgeons in particular have come to learn, at times with disastrous results, of the increased tendency for bleeding of the jaundiced patient, both at operation and post-operatively. This subject has been comprehensively discussed in the literature by many writers, among them Judd, Snell and Hoerner (1), Moss (2) and Carr and Foote (3). Various methods of therapy such as blood transfusion, calcium, viosterol, cevitic acid or Vitamin C have been instituted for the treatment or prevention of this condition in spite of the fact that earlier blood studies in jaundiced patients have failed to show any significant variations from the normal which might possibly account for this diathesis. Halverson, Mohler and Bergeim (4), Snell, Greeve and Rowntree (5), Koechig (6), Walters and Bowler (7) and Ravdin, Riegel and Morrison (8) have failed to find any appreciable change in serum calcium either in surgical or experimental jaundice, and Gunther and Greenberg (9) any clear evidence for the assumption that a deficiency of calcium exists in obstructive jaundice, or that the diffusible or non-diffusible calcium is in any way significantly altered. Even investigators such as Ivy, Shapiro and Melnick (10) who believe that a functional deficiency of calcium may exist are nevertheless of the opinion that it bears no relationship to the bleeding tendency. Studies on fibrinogen, another factor concerned in the coagulation mechanism, have shown according to Linton (11), Lewisohn (12) and Moss (2) that there is no reduction in blood fibrinogen in jaundice.

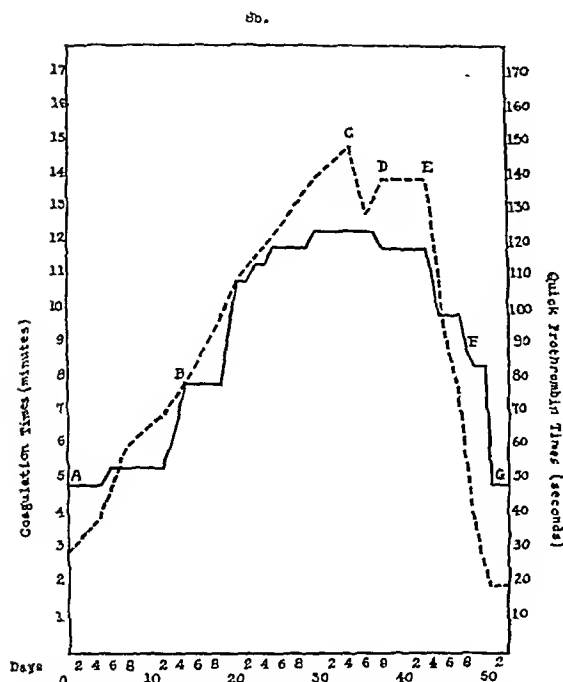
New impetus was given to the study of this hemorrhagic diathesis by the observations of Dam (13, 14) and McFarlane, Graham and Richardson (15) that chicks fed on certain diets developed a bleeding tendency and anemia. This factor, whose deficiency in the diets of chicks was responsible for the condition, has been intensively studied and isolated by Dam and Schonheyder (16, 18, 20) and Almquist and Stokstad (17) and variously designated "koagulation vitamin," antihemorrhagic vitamin, or simply Vitamin K. Exhaustive studies both chemical and physiological were conducted abroad by Dam and his associates, and by Almquist and his co-workers in this country. It was found that this chick disease, although it resembled scurvy in some respects, was not alleviated by the ad-

ministration of lemon juice or cevitic acid (19), but promptly responded when alfalfa was added in small quantities to the Vitamin-K-deficient diets fed the chicks. Almquist and Stokstad (17) found alfalfa to be extremely rich in this vitamin, and in 1936, Almquist (21, 22, 23, 24) succeeded in preparing a concentrated extract of alfalfa containing this important factor. Simultaneous with these studies, a considerable amount of work was being done on still another element in the coagulation mechanism, prothrombin, with the result that Dam, Schonheyder and Tage-Hansen (25, 27, 28) and Quick (26) found that in the hemorrhagic chick disease due to deficient Vitamin K feeding, the normal amount of prothrombin was lacking in the blood, and that the feeding of Vitamin K to these deficient animals restored the prothrombin level to normal. It was further demonstrated (25) that precipitates from the plasma of K-avitaminosis chicks were inactive as prothrombin.

This hemorrhagic diathesis is not peculiar to chicks but has been shown to exist in ducklings, pigeons, canaries, rats, guinea pigs and dogs, in which animals the requirements for Vitamin K have been studied by Dam and his associates Lewis and Schonheyder (29, 30). Recently, Roderick (31, 32) has described a disease occurring in cattle fed on spoiled sweet clover hay, in which the animals developed a hemorrhagic disease which showed qualitatively a marked reduction of blood prothrombin. This condition was cured by transfusion and by feeding alfalfa to the stricken animals. Quick (26) was able to demonstrate a quantitative reduction in prothrombin in this condition and was of the opinion that there was apparently some toxin in the spoiled sweet clover hay which exerted a depressing effect on the prothrombin (44). That apparently other toxic agents could produce a deficiency of prothrombin was shown by Smith, Warner and Brinkhous (33) who found that in experimental chloroform intoxication, a deficiency in fibrinogen and prothrombin could be produced, and that by varying the doses of chloroform, a depression in prothrombin but not in fibrinogen could be obtained, findings which seemed to indicate the role of the liver in prothrombin manufacture.

Several years ago it was suggested by Quick, Stanley-Brown and Baneroff (34) that low prothrombin values did occur in obstructive jaundice patients, although a majority of such patients showed normal figures. The relationship between the absence of bile in the intestines and a bleeding tendency had previously been noted and described by Hawkins and Whipple (35) in bile-fistula dogs. They further ob-

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Graph 1. Illustrating the effect of bile and Vitamin K on the coagulation and prothrombin times. Solid line indicates the coagulation time and broken line the prothrombin time. A. Normal values at start of experiment. See column 1 in table. B. Beginning of hemorrhagic diathesis. See column 2 in table. C. Point of severe bleeding. See column 3 in table. D. After the use of Vitamin K alone. Start of administration of bile alone. See column 4 in table. E. After use of bile alone. Start of administration of bile and Vitamin K together. See column 5 in table. F. Cessation of bleeding. G. Return to normal values. 8 days after use of bile and Vitamin K. See column 6 in table.

served that this tendency was prevented by feeding whole bile to these dogs. Hawkins and Brinkhous (36) advanced this study by showing that the bleeding in these total biliary fistula dogs was due to a prothrombin deficiency. They further confirmed the finding that bile feeding could correct this condition. Warner, Brinkhous and Smith (37) applied these observations to the study of jaundiced patients and found that no bleeding tendency was discernible when the prothrombin level was above 50% of the normal, but that when this level fell below 35%, bleeding from mucous membranes or hemorrhages at operation or post-operatively were encountered. Restoration of bile to the intestinal tract resulted in a gradual rise in the prothrombin level and cessation of bleeding. This could be accomplished by either feeding bile orally or releasing the obstruction. Quick (38) had previously suggested that this depletion of prothrombin might be due to the absence of bile acids in the intestinal tract, causing a faulty absorption of Vitamin K similar to the observation made by Heymann (39) that viosterol was not absorbed after experimental ligation of the common duct. This surmise has been further augmented by the work of Greaves and Schmidt (40) who concluded that in rats bile probably acts as a carrying agent for Vitamin K across the intestinal tract, a finding suggested by the observation of Smith, Warner,

Brinkhous and Seegers (45) that bile fistula dogs also suffer from Vitamin K deficiency as a result of bile exclusion from the gut. Warner, Brinkhous and Smith (37) were still further able to demonstrate that the addition of Vitamin K to bile feeding produced a very rapid rise in prothrombin level, with rapid cessation of bleeding. These principles were applied in several cases of jaundice with a hemorrhagic diathesis by Butt, Snell and Osterberg (41) and as a precautionary measure in cases of obstructive jaundice where the Quick prothrombin time (42, 43, 44) was not greatly elevated.

The present status then of our knowledge in this interesting field can thus be briefly summarized:

A hemorrhagic tendency exists in humans with jaundice and in experimental animals with a total external biliary fistula. Under such conditions, there is a lowering of the blood prothrombin. A similar deficiency of prothrombin is associated with "hemorrhagic chick disease" and the hemorrhagic diatheses found in other experimental animals. A like diminution in blood prothrombin is found in the spoiled sweet clover hay disease of cattle, possibly due to some toxic factor, and in chloroform poisoning which injures the liver. The "hemorrhagic chick disease" and the spoiled sweet clover hay disease can be prevented or cured by feeding alfalfa which is rich in Vitamin K. In jaundiced humans and in bile fistula dogs, there is apparently a faulty absorption of Vitamin K from the intestinal tract due to the absence of bile which is necessary for the transfer of this fat-soluble vitamin through the intestinal wall. The administration of bile alone orally when there is an adequate diet rich in Vitamin K, or the administration of bile and Vitamin K where the diet is deficient in this factor, will produce a rise in prothrombin level and alleviation of symptomatology. Vitamin A, Vitamin C and Vitamin D supplements do not correct this prothrombin deficiency (45, 46). There appears to be data suggesting the presence of Vitamin K in normal human feces in rather large quantities and in smaller amounts in the liver. It is apparently not present in human bile, but is present in acholic stools. It would seem that the normal organism obtains Vitamin K directly from ingested food or by putrefactive action of the intestinal flora on this food (41). The mechanism by which Vitamin K affects prothrombin remains as yet unknown. It is highly possible that additional factors besides Vitamin K and bile may play a part in this hemorrhagic tendency, such as some toxic factor as in sweet clover disease and chloroform poisoning, or some primary disease of the hepatic parenchyma with low bile acid production, or some depletion of the store in the liver by hepatic injury (47). Recently, Dam and Glavind (52) published some preliminary work on the intra-muscular injection of Vitamin K concentrates in several patients with obstructive jaundice and reduced clotting power with the purpose of eliminating the use of bile therapy. Their results seem to indicate that parenteral injection of Vitamin K can render the clotting power normal in these cases.

Almqvist and Stokstad (17, 48), Dam and Glavind (49, 52) and Osterberg (50) have contributed greatly to our present knowledge of the occurrence in nature and the chemistry of Vitamin K. This factor is found in such vegetables as tomatoes, kale, cabbage, spinach, the green leafy portions of plants, orange peel, alfalfa,

hog liver fat and in tuna fish meal after putrefaction. It is not found in cod-liver oil, wheat germ oil, carotene, potatoes, rice, corn, rye, wheat or lemon juice. It is fat soluble and is found in the non-sterol fraction of the unsaponifiable fat. It is not identical with Vitamin H or Vitamin D in chemical properties or physiologic action. It is unstable to alcoholic alkali, is unsaturated as well as colorless, and is fairly heat stable. It is optically inactive, has a molecular weight of about 600, and has its activity destroyed by ultraviolet. McCay's (51) description of its having no sulphur or phosphorus but a small amount of nitrogen, and that color tests indicate an indole nucleus was found to be inaccurate, inasmuch as Almquist (48) has succeeded in extracting from the Vitamin K concentrate giving these reactions a crystalline fraction which is non-nitrogenous and contains one or more benzene rings, no phosphorous, no sulphur, and no indole nucleus.

The observations of Hawkins, Whipple and Brinkhous (35, 36), on bile fistula dogs, previously mentioned, prompted us to ascertain, first, the possibility of initiating a similar bleeding tendency in a human with a total external biliary fistula; second, the time element required to develop such a diathesis under test conditions consisting of a diet deficient in Vitamin K and the omission of oral bile feedings; third, the effect on this hemorrhagic diathesis of the oral administration of Vitamin K concentrate and the subject's own bile, when used separately and in conjunction with each other; and fourth, the changes

produced in the coagulation mechanism throughout the crucial stages in the development and treatment of this bleeding tendency.

Procedure: The subject, a young female with a total external biliary fistula (53), was put on a low-fat, Vitamin K-deficient diet throughout this entire investigation. None of the bile collected from the fistula was re-fed orally. A complete hematologic study (see Table I) was made at the beginning of this regimen. Coagulation times (capillary tube method) were taken daily and Quick prothrombin times at intervals of two to four days. At the end of two weeks under these conditions, the subject began to show slight bleeding from the gums. A complete hematologic study was again taken at this time. The subject was permitted to bleed from the gums for a period of one week, at the end of which time bleeding from the tongue and vagina (not related to menstrual cycle) set in. The bleeding from all three points was allowed to continue for another twelve days, at the end of which time another blood study was made. 20 cc. of Vitamin K concentrate* (100 units per cc.) were then fed daily in divided doses for a period of four days without any remission in the bleeding. At this time, a complete blood study was done, following which, 300 cc. of the subject's own bile was re-fed orally. These bile feedings were continued for a five day period without any cessation of bleeding. A blood study was taken at this time and then 20 cc. of

*We wish to thank the Squibb Institute for Medical Research for the Vitamin K concentrate used in this study.

TABLE I

Synopsis of blood studies taken during various phases of the hemorrhagic diathesis. Compare with Graph 1

	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6
	Normal Values	Beginning of Bleeding	Severe Bleeding	After Vitamin K Alone	After Bile Alone	After Bile and Vitamin K Together
Blood Count						
Hemoglobin (grams)	14.4	14.2	14.0	13.5	13.0	12.2
Red blood cells	4,000,000	3,950,000	3,800,000	3,400,000	3,500,000	3,900,000
White blood cells	10,000	11,000	9,000	10,200	11,200	7,800
Blood platelets	260,000	270,000	250,000	250,000	240,000	250,000
White cell differential						
Polymorphs %	54	56	56	55	52	50
Small lymphos %	39	31	37	35	40	41
Eosinophils %	3	4	3	2	4	5
Monocytes %	4	5	4	8	4	4
Calcium time (minutes*)	5	5	5	5	5	5
Prothrombin time (Quick-seconds)	30	80	150	140	140	20
Coagulation time (minutes)	5	8	12½	12	12	5
Sedimentation time	1 hour	1 hour	1 hour	1 hour	1 hour	1 hour
Fragility test	.40-.32	.40-.32	.42-.32	.40-.32	.40-.32	.44-.32
Clot retraction time	Began in 20 min.	Began in 30 min.	Began in 1 hour	Began in 1 hour	Began in 1 hour	Began in 20 min.

Vitamin K concentrate and 300 cc. of bile were fed in divided doses to the subject. Bleeding from the gums, tongue and vagina ceased in five days, and a hematologic study was taken eight days after the introduction of this therapy. Table I is a synopsis of the blood studies taken throughout this study, and Graph 1 a representation of the daily coagulation times and Quick prothrombin times taken during this period.

SUMMARY

1. A hemorrhagic tendency was produced in two weeks in a young female with a total external biliary fistula by the feeding of a low-fat Vitamin K-deficient diet and the omission of oral bile feeding.

2. This bleeding diathesis was not alleviated by the oral administration of bile alone.

3. This bleeding diathesis was not influenced by

the administration of Vitamin K concentrate alone.

4. The use of Vitamin K concentrate in conjunction with orally fed bile produced a cessation of bleeding in five days.

5. The hemorrhagic diathesis produced was accompanied by an increase in coagulation time and Quick prothrombin time.

6. The bile and Vitamin K therapy returned the elevated coagulation and prothrombin times to normal values eight days after the initiation of this treatment.

7. The blood studies in this condition indicated an alteration in only the coagulation and prothrombin times.

8. The Quick prothrombin time is a more delicate index of the blood changes than is the coagulation time.

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The Factor of Occult Hepatic and Biliary Tract Disease in Some Cases of Allergy*

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SOME investigators in the field of allergy have frequently set forth their belief that anaphylaxis, on the one hand, and allergy and atopy on the other are unrelated. Other observers, however, hold the opinion that there is a definite relationship among these phenomena.

In 1910 Manwaring (1) pointed out that the pronounced fall in blood pressure, the essential feature of canine anaphylaxis, was due to an indirect pheno-

menon, the result of the explosive formation, or liberation, of depressor substances by the liver, rather than to a direct action of the foreign protein on the sensitized blood vessel. That same year Nolf (2), and later Weil and Eggleston (3), demonstrated similar formation and liberation of antithrombic substances in the isolated anaphylactic liver when perfused with a mixture of anaphylactic blood and specific antigen. Weil (4) showed clearly that the change in blood coagulability resulted from a cellular reaction of the sensitized liver. Manwaring and his coworkers (5)

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went further and found that blood drawn from the carotid artery, two to five minutes after throwing a dog into shock, showed little or no toxic action when transfused into a normal dog. If, however, the specific antigen was injected into a mesenteric vein of a sensitized dog and the shock blood collected as it escaped from the liver and then transfused into a normal dog, all the characteristic features of acute anaphylactic shock were produced in the recipient. Additional experimental data demonstrated that while various tissues in the dog can be sensitized to foreign protein, as shown by the distinct anaphylactic phenomena obtained in various isolated canine organs (6), yet the dehepatization of a sensitized dog abolishes the typical anaphylactic smooth-muscle response in the intact animal, even after massive doses of the specific antigen (7). The characteristic fall in arterial blood pressure, too, fails to follow the assaulting dose of antigen in a sensitized, dehepatized (Eck Fistula) dog (8). Finally, if the liver of an anaphylactic dog is transplanted into a normal dog, the latter will show all the characteristic features of canine anaphylactic shock following the intravenous injection of the specific antigen (5). There is good evidence that hyper-sensitiveness in man and anaphylaxis in the lower animal are fundamentally dependent on a common anaphylactic antibody (9). Further the basic reaction in both, namely, smooth muscle spasm and a pouring out of serum into the perivascular spaces, is the same.

There is even some direct evidence that the liver in man may play an important role in allergic states. The proteoepic function of the liver, as measured by the so called hemoclastic crisis of Widal and his associates (10), was often disturbed in allergy. Galup (11) found that 77% of 114 cases of asthma showed the hemoclastic crisis. This pointed, he believed, to the passage of improperly digested protein derivatives through the liver into the blood. Barber and Oriel (12), taking the estimate of the amino acid content of the blood as an index of liver efficiency in protein metabolism, found an increase in blood amino acids in a large number of patients during the acute paroxysms of allergic manifestations. They also found increased amounts in mild sensitization as well as in certain cases of eczema. Cameron (13), too, observed higher figures for amino nitrogen in all allergic cases and considered it additional evidence of liver inefficiency. Although Menagh (14) does not discuss the liver function in his cases, it is significant that he found biliary disease in 48.8% of 260 cases of urticaria and angio-neurotic edema. Liver dysfunction has been recorded in a high percentage of cases of migraine (Diamond (15) 32 of 35 cases; McClure and Hunt-singer (16) 65 of 72 cases)).

Therapeutically, the evidence of Fiessinger and Walter (17), that the autotoxic function of the liver is to a large extent dependent upon its glycogen content, has been utilized by Barber and Oriel (12). They obtained good results in allergic affections by the administration of glucose, while Urbach (18) had encouraging results from the treatment of the dermatoses by giving insulin and large amounts of carbohydrates. Doubtless on the same basis of improved liver function following the use of glucose, satisfactory results have been reported in treating asthma with dextrose alone. Thus a London foreign letter (19) reports a 17% cure in 30 cases of asthma so treated.

In 1931, we got our own first impression that liver dysfunction may play an important role in some cases of allergy. At that time a woman, 31 years of age, was seen who had had a chronic urticaria of three years standing. Therapeutic measures including elimination diets, eradication of foci of infection, administration of trypsin, injections of spleen extract and of peptone, autotransfusions, and biliary drainages failed to give relief. The only abnormal objective finding after a thorough diagnostic study was a 30% retention of bromsulphalein 30 minutes after a five mgm. per kilogram dose. In the hope that stimulation of the liver cells might afford her some relief, intravenous Decholin was started. She was given 2-gram doses in a 20% solution every other day. After the third injection, the patient noticed some relief. The same dosage was continued bi-weekly. Following the seventh dose, the patient for the first time in over three years was free of urticaria. Five additional injections were given and twenty-eight months later, when the patient was last seen, there had been no recurrence of the disease.

A short time later a female patient, age 30, was seen with a similar story of chronic urticaria of 16 months standing. Frequently the skin manifestations were accompanied by severe headaches and periods of unconsciousness. On one occasion repeated spinal tapping was required to give relief. When first seen by us she had already run the gamut of therapeutic measures. While she had no definite gastro-intestinal symptoms referable to her biliary tract, non-surgical biliary drainage disclosed the presence of gall stones. The bromsulphalein test was normal.

In the absence of any marked gastro-intestinal symptoms, and upon the request of the patient, operation was deferred and Decholin in 2-gram doses was administered intravenously every three days. Following the first two injections her hives were worse, but by the sixth her skin was entirely clear. She was very comfortable for about six weeks when she had a recurrence. At this time operation was advised and the gall bladder and stones were removed. The result was dramatic. Eight hours after the gall bladder was removed, a marked general urticarial eruption appeared and lasted about forty-eight hours. Since then, nearly seven years ago, the patient has been free of hives.

We have seen three other cases of chronic urticaria in which the removal of a diseased gall bladder (2 with stones, 1 non-calculous cholecystitis) produced a cure of the urticaria. Schur (20) reported 2 cases of urticaria relieved by cholecystectomy for cholelithiasis. More recently Goss (21), reported a similar experience in two instances: one with cholelithiasis and the other cholecystitis without stones.

The choleric action of Decholin is well established (22, 23, 24). Having seen its effect in the patients cited, we wondered whether the liver might not be playing an important role in some cases of chronic urticaria; and, by inference, in other allergic states, since it is generally believed that allergic phenomena, though present in different organs in different individuals, are basically expressions of the same pathologic physiology. Our clinical experiences with the use of Decholin in a variety of allergic states point to the liver as the organ primarily at fault in some cases. Such a view might be subject to experimental test if we had a means of determining accurately chronic

liver cell dysfunction. Unfortunately, such is not the case. Because of the multiplicity of the functions of the liver, the dissociation of these functions as affected by disease, the tremendous hepatic reserve, and the liver's active regenerative power, a single dependable function test for chronic damage is almost impossible. While a positive bromsulphalein test is likely evidence of impaired liver function, a negative or normal reading does not rule out even considerable chronic damage. Nevertheless, the 5 mgm. per kilogram dose of bromsulphalein has been useful in identifying those cases of allergy in which bile salt therapy would be indicated. In twenty-six cases of allergy treated with satisfactory results, eight failed to show abnormal dye retention (more than 10%). On the other hand, of forty-one cases of allergy that failed to show any response to Decholin therapy, only one showed a 20% dye retention after the bromsulphalein test. In the successfully treated group were five cases of chronic urticaria, three of bronchial asthma, 1 of chronic eczema, 3 of autumnal hay fever, 8 of intestinal allergy, 2 of chronic generalized pruritus, and 4 migraine. Those that failed to show any benefit from adequate Decholin therapy (twelve to twenty-four doses of 2-grams each) included 8 cases of urticaria, 9 of bronchial asthma, 8 of hay fever, 3 of generalized pruritus, 6 of intestinal allergy, and 7 of migraine. Of these, one of the cases of intestinal allergy had shown bromsulphalein retention.

Miss D. B., age 35 years, illustrates the successful results obtained in the hay fever and urticaria group. She had been subject to severe hay fever for eleven years prior to treatment as well as to attacks of marked urticaria after eating shell fish. Treatment with intravenous Decholin was begun on September 8, 1933, during the height of a hay fever attack. Between September 8th and 29th she received 10 doses of the 20% solution. On September 29th, the patient for the first time during hay fever season was able to go on an automobile ride. She remained free of hay fever and after the 13th dose, about ten days later, deliberately exposed herself to a field of ragweed to which she was especially sensitive. No reaction. After the 15th dose of Decholin, on October 14th, she tried a shore dinner which included shell fish and shrimps. No sign of hives. Patient has since indulged freely in all forms of sea food without the slightest ill effect. She was given in all sixteen doses of intravenous Decholin. Without any additional treatment she remained free of hay fever and hives until October, 1937, when she thought she had some slight hay fever symptoms. Two doses of Decholin at 3-day intervals sufficed to give complete relief for the rest of the season. A similar episode occurred in the hay fever season of 1938, which was again controlled completely by three doses of the drug. Before the Decholin therapy, the orthodox method of pollen desensitization was tried for three years without any relief.

B. L., age 20 years, male, had at the age of one developed a severe eczema involving the face, arms and thighs. This continued until he was six years old. At this time he developed occasional asthmatic attacks which continued until the age of twelve. Between 12 and 18 years, he was apparently free of any allergic manifestations. The asthma then reappeared and the attacks increased in severity and frequency. Asthmatic attacks rarely occurred during the day, the usual onset

being between 4 and 7 A. M. Relief was obtained either by adrenalin nasal spray or by injection. He had lost some 10 pounds in two years. A complete study of the skin reactions showed a skin sensitivity severe, moderate, or mild to 36 foods, a number of pollens, trees, animal epithelium, tobacco, and house dust. There were no discoverable foci of infection. A month's trial of diet carefully eliminating the skin sensitive foods, tobacco, and proper attention to pillow and mattress contents failed to give any relief. A complete diagnostic survey failed to yield any other abnormal findings except at 35% dye retention after the 5 mgm. per kilogram dose of bromsulphalein. Following the failure to obtain any result with the above regime, intravenous Decholin was started in doses of 10 cc. of 20% solution three times a week. After the 6th dose, some improvement was noted. Following that, improvement was rapid and after the 18th dose of Decholin, all attacks of asthma ceased. There has been no recurrence in the seven months that have elapsed. The patient has regained 7½ of the 10 pounds lost.

What then is the basis for the relatively rapid and lasting good results in some cases of allergy following the removal of a diseased gall bladder or stimulation of the hepatic cells? While we have no convincing proof, we believe for the present the following may be applied as a working hypothesis:

The liver is a filter and a detoxifying organ. Ordinarily, ingested proteins are broken down to simple compounds. Under certain conditions it is probably true that more complex fractions of the protein molecule, or even of the undigested molecule, may pass through the intestinal mucosa. To what extent this may occur has been demonstrated by Hettwer and Kriz in guinea pigs (25). They found that increasing intra-intestinal pressure could cause a rapid absorption of undigested horse serum sufficient to induce symptoms of anaphylactic shock in previously sensitized guinea pigs or to sensitize normal guinea pigs. Under certain conditions it is conceivable that inadequately split protein products will pass the human intestinal mucosa.

In such instances, if the liver is normal in its functions as filter and detoxifier, these protein products will be held and rendered innocuous. Should the liver cells be ineffective in these functions, however, enough of such protein products will through the general circulation reach various organs and there may act as the sensitizing dose. Subsequently, should the same protein under similar conditions reach the liver and pass over into the general circulation, the sensitized organ will react. Treatment of the liver with an adequate liver cell stimulus does not affect the sensitized organ but in converting the liver from a sieve to a filter, it prevents the allergen from reaching the sensitized tissue.

Where the removal of a diseased gall bladder produces prompt recovery from urticaria, we suggest that the diseased gall bladder acted as a source for the specific allergen, coupled with a poorly functioning liver. In those instances in which removal of the gall bladder is followed by a delayed recovery, it is conceivable that residual biliary tract disease may be supplying the allergen. Recovery in these cases is again not a change in the sensitized organ nor even an alteration in the permeability of the liver, but a removal of the supply of the allergen. In instances of

delayed recovery after gall bladder removal, liver cell stimulation, if our hypothesis is correct, should be employed as additional therapy.

SUMMARY

Experimental anaphylaxis in the dog yields adequate evidence for the role of the liver in the shock produced in this animal. There is also some indirect evidence in the literature of human allergy that disturbed liver function may play an important part in some cases.

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An Interesting Case of Ascariasis

By

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IT is well known that round worms may be found in any organ they can enter from the intestinal canal, such as the common bile-duct, appendix and upper respiratory tract. The following case is interesting because of the different diagnoses made and the treatments prescribed, the large number of worms present, and the roentgenographic visualization of a worm in the duodenum.

The patient was a nurse, single, 40 years of age, and was seen by me in November, 1935. The appendix was removed while she was in training. In 1919 a ventral suspension of the uterus was done, and in 1925 a cholecystectomy for stones. She worked fairly steadily as a hospital nurse for 15 years. In 1931 she was injured in the left breast by an ice box door and a hematoma formed. Ligation of the breast vessels was done to control the increasing size of the mass. About a year later she was seized with a severe pain in the same breast. Shortly after this she complained of distention and pressure in the upper abdomen, her stomach becoming intolerant to foods, and even water causing her to vomit. The diagnosis was made of pyloric adhesions due to her former abdominal operations. In 1932 she was operated on for these adhesions. Following this she rapidly lost weight (30

lbs.), vomited more persistently, became unable to work, and complained of a constantly moving sensation in her stomach, "a feeling as if there were mice in the stomach." X-ray examination disclosed gastric stagnation, food remaining in her stomach for "over seventeen hours." A gastro-enterostomy was done in June, 1933. Three days after this operation there developed a phlebitis in the right lower extremity and then in the left. She continued to vomit and do badly. Although the gastro-enterostomy stoma seemingly was functioning properly the gastric stagnation was not much lessened. Ten weeks after the gastro-enterostomy she started vomiting round worms, bringing up from two to eight each time she vomited. She stated that in the course of ten days, she vomited over 200 worms and passed an occasional one by rectum.

In 1933 a diagnosis of probable pregnancy was made because of sudden cessation of menstruation and a serous discharge from both nipples. Because of a "terrific" pain in the left arm and breast she was examined by Dr. Hunner of Baltimore, and two strictures of the left ureter were diagnosed. For this the right kidney was removed. Shortly after she complained of pain and noticed "lumps" in both breasts (notably the left) with discharge from both nipples, and both breasts were removed. The pathological diagnosis was

chronic mastitis. Between the time of the removal of the kidney and breasts, several X-ray examinations of the stomach were made, one in July, 1934 "showed evidence of worms in the pylorus" with gastric stagnation. She continued to vomit an occasional worm and in October, 1935, had much difficulty getting her bowels to move. Ova were found in seventeen of thirty-one stools.

When seen by me she weighed 76 lbs., having lost practically 50 lbs. since the beginning of her illness. She stated that she was losing "three out of four

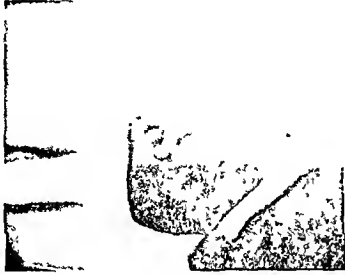


Fig. 1

meals," the food "came up automatically and she had no control over it." If the breakfast was not ejected, the second meal would remain down but in the evening she would vomit all the meals of the day at one time. The vomiting was more pronounced after taking alkalies or santonin, the latter drug having been taken more or less steadily for several years. She stated that the last worm she had vomited had come up a month previously and as a result of several negative stool examinations for ova and X-ray films of the stomach no more were thought to be present. Altogether she thought that she had vomited over 500 round worms, and passed about 50 by rectum.

Laboratory findings: Stomach achylia. The stools contained an occasional ovum of *ascaris lumbricoides*.

She presented films taken by Dr. Barlow J. Hynes of Rockville Center, L. I., which showed the presence of a moderate sized round worm coiled up in the duodenum. (See Fig. 1)

Because of the poor general condition, effort was made to increase her vitality. She was placed on a bland low residue diet with vitamins and minerals, rectal instillations of 25 per cent glucose solutions, rest and hyperdermic injections of calcium and iron glycerophosphates.

As a result of this treatment she gained 15 lbs. in weight and was considerably improved. Two films showed the worm still in the duodenum. Several attempts were made to remove the worm, it of course not being known whether there were others present or not. Naphthalin in 0.05 doses, 4 times a day, Oil of Chenopodium in 5 minim doses, both proceeded by purgation was tried. These treatments were fatiguing and could be persisted in for only a few days. After these a film showed the worm still in the duodenum.

February 10, 1936, Dr. P. D. Lamson, et al (Am. J. Hyg., Vol. 13, No. 2, Page 568, March, 1931), suggested the use of hexylresorcinol in crystalline form for ascariasis claiming that no symptoms of importance followed its administration and that its use was safer than carbon tetrachloride or tetrachlorethylene. Following an evening meal of soft foods, 5 crystals (1 gm.) of hexylresorcinol (Sharp and Dohme) was given the next morning on an empty stomach in one dose with a glass of water, a saline purge given the next morning. On the 3rd day she passed a single adult female worm and two subsequent X-ray examinations proved that the worm had disappeared from the duodenum. After this the stools were examined for ova twice a week for six weeks. Each was negative for ova and they have remained so for nearly two years. In the meantime the patient recovered her health and strength, weighing 120 lbs. on January 3, 1939, and is working steadily and hard as a district nurse in Nassau County, New York.

Editorials

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ERRATUM

In the paper by Mandred W. Comfort, Robert L. Parker and Arnold E. Osterberg, on "The concentration of pancreatic enzymes in the duodenum of normal persons and persons with diseases of the upper part of the abdomen," which appeared on page 249 of the June issue of this journal, an error occurred in the values for trypsin. All values for trypsin as they were given should be multiplied by the factor 2.4 in order to obtain the correct values.

HOW OFTEN IS THE DIAGNOSIS OF AN ABDOMINAL NEUROSIS CORRECT?

EVERY gastro-enterologist will be interested in a paper recently published by Wilbur and Mills (Ann. Int. Med., 12:821, Dec., 1938) in which they report efforts to check the accuracy of the commonly made diagnosis of digestive neurosis. Every physician who sees many patients with gastro-intestinal symptoms will every day make one or more diagnoses of a functional disorder. Often the patient will resent this diagnosis and will be dissatisfied with it. Often he or she will refuse to accept it and will shop around for a time in the hope of finding some physician who will make a diagnosis of organic disease.

In order to see how often well trained physicians are likely to be correct in their diagnosis of a functional or nervous indigestion, Wilbur and Mills reviewed the records of 354 patients who returned to The Mayo Clinic for a check-over some years after they had been told there that they were suffering from a functional disorder. The minimal interval was more than five years and the average interval was 7.3 years. The results of the study indicated that the original diagnosis was correct in at least 85 per cent of the cases. There were 39 cases in which organic disease of the gastro-intestinal tract was found at the second examination. In 19 of these the final diagnosis was duodenal ulcer. A few gastric ulcers were found. There were 3 cases of cholecystic disease and two of carcinoma of the stomach. Of course, one cannot be sure that the disease on the subsequent examination was present when the patient first went to the Clinic, but in many cases the fact that the symptoms com-

plained of at the second visit were those described at the first visit indicated that a mistake in diagnosis had been made. There were a few cases of pernicious anemia and cardiac disease in which the diagnosis was probably missed at the first examination.

One conclusion drawn by Wilbur and Mills was that the diagnosis of an ulcer-like functional syndrome should now be made with reluctance. Probably now that the gastroscopist has come forward to help us we gastro-enterologists will not so often fail to recognize the presence of the shallow type of gastric ulcer which the roentgenologist can hardly hope to see. The outstanding conclusion to be drawn from this important paper is that when well trained men make the diagnosis of functional indigestion they are correct in a high percentage of cases.

Walter C. Alvarez, Rochester, Minn.

DIAGNOSIS OF DISEASE OF THE PANCREAS

THE pancreas is one of the few abdominal organs which has been inaccessible for roentgen exploration. However, some progress has been made in the detection of early changes in the duodenum, secondary to disease of the head of the pancreas. Changes in the mucosa of the descending portion of the duodenum has been previously ignored by the roentgenologists. It has only been recently that our attention has been focused upon abnormal mucosal configuration which has made it possible to disclose small and early lesions of the head of the pancreas, which frequently produce secondary changes in the duodenum. Frostberg in 1938, and Feldman in the last issue of the American Journal of Digestive Diseases calls attention to a new roentgen sign produced by pressure on the ampullary portion of the duodenum, elicited roentgenologically by an inverted three filling defect, which is indicative of swelling of the head of the pancreas.

It is probable that a more direct method of examination of the pancreas and the biliary ducts will become feasible in the near future. Imperatori recently reported studies on intubation of the duodenum by means of a duodenoscope, in which after the injection of an opaque medium into the duct he could radiologically demonstrate the common bile duct and the Duct of Wirsung. The new method of investigation opens up a vast field for the diagnostic exploration of the pancreas and biliary ducts. It is hoped that this method will be further developed into a practical procedure for the study of the pancreas.

Maurice Feldman, Baltimore, Md.

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A FINE RÉSUMÉ OF RECENT GASTRO-ENTEROLOGIC ADVANCE

AMERICAN gastro-enterologists who have not yet read it will greatly enjoy and profit from a reading of the excellent review of gastro-enterologic literature (from January, 1937, to June, 1938) published by Chester M. Jones and his associates in the October

number of the Archives of Internal Medicine. It is well written and full of valuable information. We wish we could reprint it here in toto.

Walter C. Alvarez, Rochester, Minn.

THE CLINICAL USE OF AN IMPROVED METHOD OF GASTRIC ANALYSIS

IN the September, 1938, number of the Journal of Clinical Investigation, Welch and Comfort reported results obtained with the use of the type of test meal advocated by Wilhelmj, Neigus and Hill. With this test meal it is possible to follow the progress of secretion in the stomach and to estimate the acidity of the juice secreted instead of the acidity of the usually studied mixture of gastric juice and food and regurgitated duodenal secretions. The method permits one to follow the reduction in concentration of acid chloride during the latter half of the test period, also the appearance of an excess of acid or alkali in the combined fluids that enter the stomach.

Unfortunately the method does not permit measurements of the total amount of acid secreted, of the total amount of alkali that enters the stomach, or of the total neutralization of acid chloride during the test period. It does give a good idea, however, of the effectiveness of duodenal regurgitation in lowering the acidity of the gastric contents. Such regurgitation was observed repeatedly in the patients studied.

The relative importance of the factors concerned in the regulation of acidity of the gastric contents appeared to be different in normal persons and in patients with duodenal ulcer. In normal persons the alkaline element of the gastric juice was more important than the acid element, whereas the reverse was true in most of the patients with duodenal ulcer. Largely because of this, the final dilution of the juice tends to be 100 per cent effective in normal persons, while it rarely is so effective in cases of duodenal ulcer. The volume of acid secreted by the fundus of the stomach seemed to be greater in cases of duodenal ulcer than in the case of normal persons.

Walter C. Alvarez, Rochester, Minn.

A DEPRESSANT TO GASTRIC SECRETION FOUND IN SOME GASTRIC JUICES

AT the meeting of the Central Society for Clinical Research held in Chicago, November 4 and 5, 1938, Dr. Alexander Brunschweig, Dr. John Van Prohaska, Dr. T. H. Clarke and Dr. Ernestine Kandel reported that in dogs with subtotal gastric pouches and the nerves and vessels intact, the intravenous injection of neutralized gastric juice from the same animal or from other dogs produced no effect on the secretions of the pouch, but the injection of gastric juice from nine out of twelve patients with pernicious anemia produced periods of achlorhydria. The same thing happened with the juice from three out of six patients with gastric cancer. Juice from three out of sixteen patients who did not have pernicious anemia or gastric cancer also produced achlorhydria in the dogs. Boiling

the effective juice for ten minutes destroyed its power to suppress secretion in the dogs.

Walter C. Alvarez, Rochester, Minn.

PECULIAR RACIAL DIFFERENCES IN INCIDENCE OF GASTRIC LESIONS

BONNE, Hartz, Klerks, Posthuma, Radsma, and Tjokronegoro (Am. J. Cancer, 33:265-279, 1938) have been interested in the striking difference in frequency of gastric ulcer and gastric cancer as observed in Malays and Chinese living in Java and Sumatra. This difference has been observed by every pathologist working in these islands. The incidence of both diseases is remarkably low among the Malays, whereas among the Chinese it is about the same as that observed in the western world. The authors have tried in vain to correlate this difference with differences in diet and differences in temperament.

This first paper of a series reports the writers' inability to find any morphologic or physiologic differences in the stomachs of the individuals of the two races. It was found that the incidence of gastritis and erosions was about the same in the stomachs of the two groups of people. The acidity averaged perhaps a little higher among the Malays, who are largely immune to ulcer. No difference could be seen in the amount of duodenal regurgitation. The wise conclusion reached was that the freedom of the Malays from gastric lesions must be due to the absence in them of some deleterious factor that is at work in Europeans and Chinese.

Walter C. Alvarez, Rochester, Minn.

DOES DISTENTION OF THE BOWEL IN CASES OF INTESTINAL OBSTRUCTION START A VICIOUS CIRCLE BY INCREASING SECRETION?

EVERYONE who is concerned with the problems of intestinal obstruction will read with interest a paper by M. L. Montgomery in the Proceedings of the Society for Experimental Biology and Medicine, November, 1938, page 382. It has long been a question whether or not distention of the obstructed bowel will bring about an increased secretion of intestinal juice and in this way produce more distention. Work by Swindt and Montgomery showed that in an isolated duodenojejunal loop a strangulating type of obstruction depressed the secretion in stomach, pancreas, liver, and duodenum. This depression came promptly and lasted for from twelve to twenty-four hours, after which the secretion returned toward normal and then decreased again as the animal became moribund.

These experiments have now been repeated by Montgomery using also a denervated loop of bowel. Both loops were distended by a balloon and suppression of the combined digestive secretions was observed only in the normal loop. The impression was that in intestinal obstruction distention of the loop does not start a vicious circle due to the increase of secretion.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

Son of Old Man Hot. By Walter Dyk. Harcourt, Brace and Company, New York, 1938, pp. 378. Price \$3.50.

EVERY thoughtful physician worthy of the name should be and must be somewhat of an anthropologist and ethnologist. He must be interested in the workings of the human mind, and he must be interested in everything that concerns humanity.

Such physicians will be interested, then, in the few remarkable autobiographies of primitive men that have appeared in recent years. One remarkable one was the life of an old medicine man from darkest Africa. Another was the life of an old American Indian who watched the coming of the white man into the country north of the Yellowstone. Now Walter Dyk has given us the fascinating story of a Navajo Indian who tells of his boyhood in the Southwest. It shows that there isn't much difference between the mind of the primitive and the cultured man. It throws much light also on the sexual awakening and the sexual life of the American Indian before he had much contact with the white man.

The Pathology of Diabetes Mellitus. By Shields Warren. Philadelphia, Lea & Febiger, 1938, 246 pp. Price \$4.75.

THIS is a splendid book. Would that all scientific texts were as well written, illustrated and published. Every medical librarian will want to get a copy.

As every internist knows, the use of insulin is now keeping alive thousands of persons with severe diabetes. It is keeping them alive long enough so that they can die of arteriosclerosis and other troubles. Years ago the physician had to spend all his energies trying to keep his diabetic patients from dying in coma; now he has time to think of guarding them so far as is possible from the results of the chronic degenerations which are taking place in their arteries, their eyes, and other parts of their bodies.

This book is a most timely one in that it reviews briefly and authoritatively everything that is known about the pathology of the disease. Dr. Warren bases his statements not only on the large autopsy and biopsy material that has been accessible to him, but also on material which he obtained from pathologists all over the country. He has also searched the literature, and there is a good bibliography at the end of every chapter. The book is beautifully illustrated and attractively printed, and Dr. Warren and the publishers are to be congratulated.

It's More Fun to Be Thin. By Jean Z. Owens. Boston, Marshall Jones Company, 1939. Price \$2.00.

THIS appears to be one of the best of the books on reduction diets written by lay persons. As usual with such books, the author looks on the amusing side of the problem and is inclined one minute to tease her patients and another minute to try to get them into a good humor. She starts out by warning against the use of dangerous reducing drugs. She cleverly exposes the tendency of many women to kid themselves into

feeling that they are not really very fat. She tells of the woman who, when she goes to buy a dress, insists that she be sold a thirty-six, which she can't possibly get into. Finally the wise sales girl brings out a forty-four which she says is a thirty-six but probably slightly over-size.

One of the best chapters in the book is one in which she shows the stout woman how she can make up menus which will allow her to eat what she must eat without at the same time forcing the family to reduce. Actually, many a woman will find it too much of an effort to prepare two separate menus for each meal, one for herself and another for the family. A woman tends either to eat too much with the family or else to get the family on the rampage because of a restricted diet.

The author is frank in admitting that most women diet not for reasons of health but to hold on to a husband or to try to become more attractive to some eligible male.

One excellent bit of advice to those who are dieting is never to mention the fact. Friends, relatives and bridge partners will certainly agree that this is good advice. Another good bit of advice is that the patient watch his disposition as well as her calories and her weight. Many women complain that of course they can reduce but it makes them feel too mean and quarrelsome.

Finally, the author advises wisely that no woman reduce more than 10 pounds without the advice and guidance of a physician. Women who start on a reduction diet must realize clearly that they are not going to spend a few weeks at it and then quit. They must settle down to change their habits of eating and to change them *permanently for life*. They must come to look on whipped cream much as an orthodox Mohammedan looks on pork; it just isn't for him and never will be.

Clinical Gastro-Enterology. By H. W. Soper. St. Louis, C. V. Mosby Company, 1939, 314 pp., 212 illustrations.

ANY book from the pen of Horace Soper will be read with interest by all American gastro-enterologists because they know him and like him and respect him as a man and as a physician. Dr. Soper states that his idea was to cover the field of gastro-enterology with particular emphasis on diagnosis and treatment. The book was written not only for the specialist but for the internist and the general practitioner. Dr. Soper wanted also to clarify a subject which he thinks has become entirely too complex.

As one would expect to find, there are many signs of clinical wisdom scattered through the book, and about the only criticism that we would feel like making is that an attempt was made to cover too large a field in too small a space. It is hardly possible any more to cover the field of modern gastro-enterology in 314 pages, no matter how skilful or how great an effort the writer makes to condense his speech. Worse yet, a large part of this book is taken up with illustrations.



Every doctor has patients whose philosophy of life is "Eat, Drink, and Be Merry" The second part of this quotation, "For Tomorrow We Die", is rarely accorded even a moment's thought by those who enjoy what they call "good living" That is why it is difficult to enforce a sensible regimen in the management of patients whose pathological conditions are due to indiscretions in eating and drinking One order, however, which most patients will gladly obey is to drink Vichy-Célestins, and many physicians have found this mildly alkaline natural mineral water a useful adjuvant to their regular therapy We suggest that you order a glassful morning and night in cases of hepatic, biliary, gastrointestinal, urogenital, and metabolic upsets Vichy-Célestins has a delightfully pleasant sparkle, although it is not heavily charged with CO₂ It promotes secretion and fluidity of bile, favors normal pH of the blood, and is not a laxative For further information about Vichy-Célestins please write to AMERICAN AGENCY FOR FRENCH VICHY INC 285 MADISON AVENUE, NEW YORK, N Y

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One has the feeling, therefore, that although the book may be of interest to the specialist, it would not be of great value to the general practitioner because its information is too sketchy. The general practitioner or the beginner wants detailed information. Perhaps in subsequent editions Dr. Soper will make a much better book by either cutting down on the number of subjects discussed or else tripling the number of pages.

Sex Life in Marriage. By Oliver Butterfield. New York, Emerson Books, Inc., 1939, 192 pp. Price \$2.00.

Our impression from reading this book is that it is the best of the many

we have seen. Mr. Butterfield has discussed a difficult subject in a beautiful way. Although he has gone much farther than many writers of such books have done in the way of describing things in detail, he has used such beautiful English and has breathed such a fine spirit into it all that even the most prudish woman could hardly take offense. We did not see anything that we would want changed, and we believe this is a book which can safely be handed by physicians or ministers or parents to any young man or woman who is contemplating marriage. It would be a wonderful thing if it could be handed to every couple who, because of sexual

incompatibility, are contemplating divorce.

Hemorrhoids. By Marion C. Pruitt. St. Louis, C. V. Mosby Company, 1938, 170 pp.

This is a most attractive book, beautifully illustrated, with several plates in color. First there is a good chapter on the anatomy of the anal region. Then there are chapters on the instruments used by the proctologist, and on the etiology and pathology of hemorrhoids. There is much detailed information on these troublesome lesions and on the way in which they should either be injected or removed. Everyone who has to treat hemorrhoids will profit by reading this book.

Manual of Toxicology. By Forrest R. Dnvison. With a foreword by David Murrin. New York, Paul B. Hoeber, Inc., 1939, 241 pp.

This is a handy little volume of 241 pages. The articles are short and snappy, and each chapter has a bibliography. This would be a good book to have around a doctor's office for consultation in cases of emergency.

Endocrine Therapy in General Practice. By E. L. Sevringhaus. Chicago, Year Book Publishers, Inc., 1938, 192 pp. Price \$2.75.

In these days of rapid advance in the isolation and synthesis of many powerful hormones, there is great need for a handy volume which will help the physician to find his way through the maze of new terms, and which will give him concise and trustworthy information. As Dr. Sevringhaus points out, advance in knowledge is taking place so rapidly in this field that no book can be up-to-date even when it is published. Within a year it is likely to be still more out of date. Unfortunately, also, most men today are using endocrine products without much knowledge of the indications for their use or knowledge of how they may act. Many are reporting their results without sufficient logic and with unjustified enthusiasm. They are rushing in where angels would fear to tread.

Dr. Sevringhaus and his associates have for years been doing extensive research in an effort to find out how the several secretions from pituitary and ovary wax and wane in amount during the monthly cycle through which every young woman passes. He therefore is highly competent to write on the subject, and this makes it all the more significant that on almost every other page of the book he admits his inability to give any answer to some important question.



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It is highly probable that during the next ten years we are going to see a great deal of harm done both to men and women through the unwise use of tremendous amounts of the powerful new hormones which are now coming on the market. As Dr. Sevringhaus and others have pointed out, the giving of some of these hormones depresses the function of and injures the very organ, such as ovary or testicle, which the physician is trying to help. Large doses of ovarian hormones can lead to the production of a large and cystic ovary. They can destroy the follicles. Similarly, in man the giving of large doses of testosterone can put a stop to spermatogenesis and can injure the testicle.

Actually, much evidence indicates now that in many cases of defective menstruation one should not give the ovarian hormone but should rather give the gonadotropic or ovary stimulating hormone which comes from the pituitary gland. Similarly, much of the giving of hormones to sterile women is not logical but is likely to do as much harm as good. Many women are being given today large doses of ovarian hormone when actually a laboratory test would show that their ovaries are already forming more than they need. Unfortunately, as Dr. Sevringhaus points out, many of the methods now available for the assay of these hormones in urine or blood are so complicated that they can be used only in research laboratories, and then it is as yet impossible for the research worker to tell always what the results mean. But with all Dr. Sevringhaus' admission of ignorance this is an excellent book. It is the better and the more trustworthy because it is so full of admissions of ignorance.

End-results in the Treatment of Gastric Cancer. By E. M. Livingston and G. T. Pack. New York, Paul B. Hoeber, Inc., 1939, 179 pp.

This is an attractively written, illustrated and published volume summarizing an immense amount of work done in reviewing the world's statistics on the results of the operative treatment for carcinoma of the stomach. It is based on a study of 14,000 gastric resections reported in the literature. The essential conclusions are that cancer of the stomach can be cured and is being cured by gastric resection when this is carried out early. Perhaps one out of five of the persons who survive a well done resection of the stomach are alive five years later. Those patients who recover are usually perfectly well.

Largely because of the fact that only one in four patients with carcinoma of the stomach can have a resection with any hope of cure, and only one in five remains well, only one in twenty of the group as a whole can hope to be saved.

Unfortunately the number of gastrectomies for carcinoma of the stomach performed each year is very small, except in the largest surgical institutions. This fact, of course, adds greatly to the mortality rate, which in some institutions is reported as high as 50 per cent. Under the best of conditions it appears to be around 17 per cent. Mortalities reported in

the neighborhood of 5 per cent are for resections for benign ulcer. The average mortality for resection of gastric cancer based on figures from many clinics is around 30 per cent. As the authors state, "No surgeon who is unqualified or who has not the full intent to resect a gastric carcinoma if a resectable tumor is encountered has the moral right to operate on a patient with gastric carcinoma." The surgeon does no service to the patient when he performs only a gastro-enterostomy because this adds, on the average, only two months to an unhappy life.

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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

authors had hammered home the fact that if better results are ever to be obtained patients must not be temporized with and given treatments for ulcer by physicians—as they are now being given—for periods averaging eleven months.

Vitamin B₁ and Its Use in Medicine. By R. R. Williams and T. D. Spies. New York, The Macmillan Company, 411 pp., 1939. Price \$5.00.

This book should for a time end the writing of books on Vitamin B₁ because it is so good and so authoritative, so complete, and so well documented. It was produced through the collaboration of the chemist who isolated the vitamin and a physician. The first part deals with the history of the subject and its medical aspects. The second part takes up in detail the isolation of thiamin, the study of its chemical composition, the methods of assay, the synthesis, the distribution of the substance in foods, its requirements in relation to body weight and the intake of the various constituents of food, its relation to carbohydrate metabolism, and the way in which it probably acts in living tissues.

The book is well written and so interesting that one can sit down and read it like a fascinating story. Obviously it is a book that will have to be

added to every library of any size and to the library of every studious dietitian.

Incidentally, there is a delightful article on Robert R. Williams, written by R. E. Gruber in the April, 1938, number of the Chemical Bulletin published by the Chicago Section of the American Chemical Society. In this brief biography one learns that Robert Williams was working in Manila some twenty-five years ago when Dr. Vedder gave him a bottle of rice polish extract saying "There is something in this syrup which cures infantile beriberi. Find out what it is and if possible see if you can't make it in the laboratory." Stimulated by this challenge, Williams began in 1910 to hunt for something which he later found was present in about 40 parts per million of the rice polishings. Year after year, working always in spare time and often in his kitchen or his garage, Williams kept on the trail of the elusive substance until finally in 1933 he was able to get out about 5 grams of pure vitamin per ton of rice polishings and to secure some 12 grams of crystals. Then there were years of hard work before the structural formula could be determined and the synthesis could be made. Finally came the tense and dramatic moment when after twenty-five years of hard work the new

synthetic substance was injected into sick rats, and finally came the answer, "The rats say yes." Many research workers flit from one problem to another, but occasionally one finds a man like Williams who doggedly follows one trail for most of his life until he runs down his quarry. We need more such men.

Chronic Diseases of the Abdomen. By C. Jennings Marshall. Little, Brown and Company, Boston, 1939. Price \$6.00.

We have often wished that books on diagnosis were based more on the writer's personal experience and less on what he could glean from the literature. What a man has derived from his own experience is usually correct and worth studying by others, but what he gets from the literature is commonly wrong. This is a book which bears all the marks of being based on an enormous experience in clinic and hospital. The book is well illustrated, and any physician who will read it and digest it carefully will have given himself a good graduate course in the diagnosis of abdominal lesions.

Abstracts

WATERMAN, L.

Hydrochloric Acid Secretion in the Stomach of Hypophysectomized Rats. Acta Brevia. Veerland., Vol. 8, p. 182, 1938.

Gastric contents of 192 hypophysectomized rats were examined. In 27% of the animals the stomach was found to be empty and no acid juice was secreted. However, if the stomach of these animals were filled with food, hydrochloric acid could always be demonstrated in the contents.

Consequently, although pituitary extracts may give an increased gastric secretion, hypophysectomy is not necessarily followed by achylia gastrica.

M. H. F. Friedman, Detroit.

CONNOTATIONS

H. J. SIMS, M.D.
Denver, Colorado

Hippocrates recognized empyema. He instructed that the incision be made at the seat of the greatest pain and swelling. The opening was to be kept open by a teat and the daily injection of wine or oil. He remarked that the patient recovered within 40 days or passed into phthisis. The teachings of Hippocrates are quoted in the writings of Celsus and Galen. Fabricius later revived these teachings. It is recorded that Euryploa from Knidos saved the life of Kinias by opening his chest with a red hot iron. In the early part of the

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*An interesting Editorial on this material appeared in the March issue of The American Journal of Digestive Diseases, entitled, "Aids to Normal Bowel Function," authored by Dr. J. Arnold Bergen of Rochester, Minnesota. Reprints will be supplied upon request.

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eighteenth century, Pouteau, David, and Calisen accepted the teachings of Hippocrates. To Mosler of Griefswald, Koch of Darpart, and Bull of Christiana, is due the credit for systematic experimentation and development of the operative technique. Mosler in 1872 advised irrigation of the thoracic cavity with a solution of potassium permanganate. Hellier substituted a solution of corrosive sublimate. History records that Bary in 1726 and Herff and Hooker later used a solution of corrosive sublimate. Figueira, Pinncy, and Mackey in 1875 recommended solutions of carbolic acid. The use of a trocar was popularized by Bowditch in 1852. Playfair in 1875 advised the use of aspiration. Dieulafoy and Potain further improved the method with special aspirators. Bulau in 1891 introduced both siphonage and drainage. Perthes devised a water pump for mechanical drainage; Nordmann in 1907 devised continuous suction. Roser in 1865 suggested rib resection; eleven years later Hewitt advised the use of drainage tubes.

Anthony of Augusta, Georgia, first executed a pneumectomy in 1823. To Gluck, Marcus, Block, Schmidt and Biondi is due the summary of the knowledge of pneumectomy up to 1887. Their work was confined to animal experimentation. Kronlein was probably the first to deliberately remove a portion of the human lung. His patient was a female, eighteen years of age who suffered from a sarcoma of the sixth rib. Weinlechner's patient suffered from a myxochondroma of the right chest wall, with the lung. Ombone's case was a self-inflicted wound of the right chest. Ruggi in 1885 reported two attempts with fatal results. Block attempted bilateral pneumectomy on a patient who, he believed, suffered from double apical lesions: death followed. When medico-legal inquiry did not reveal the pathology he suspected, he found solace in suicide. In 1891, Tuffier reported a successful pneumectomy on man through an intercostal incision. Lawson in 1893 described a successful removal of tubercular apex. Heidenhain in 1898 removed the left lower lobe for bronchiectasis.

Neve, as early as 1887, practiced pneumotomy. Tuffier of France, proposed separation of the parietal peritoneum to avoid opening the pleural cavity. Roux in 1891 proposed uniting the two layers of the pleura with sutures. Piorry carried out compression of the chest to restrict movements of the chest and thereby to secure adhesions of the pulmonary and costal pleura. Mosler in 1885 collected 84 cases submitted to pneumo-

tomy with a mortality rate of 32 per cent. Frzbicki in 1892 recorded 24 cases not mentioned by Mosler.

Estlander in 1877 introduced the method of multiple rib resection for chronic empyema. Some doubt exists as to whether he independently contrived the operation. Gayet most probably originated the idea which was demonstrated by Létiévant. Schede of Hamburg modified the technique of Estlander. Depage further modified Schede's method. Delorme and Fowler proposed liberating the lung by removal of the dense layer of scar tissue. Ransohoff practiced pleural dissection. Dowd combined the method advocated by Fowler and Delorme.

Fenger in 1882 performed the first thorocoplasty in America.

Michael Entmuller in 1667 concluded from the experimental work of Tecop that no medicines will dissolve gall stones and even when they appear gone others may recur and lead to death.

Pliny, the Elder, recommended the kidneys of rabbit cooked in wine as a remedy for bladder stones.

The papyrus of Ebers, written approximately 300 years before Moses was rescued from the bulrushes described four blood vessels distributed to the nostrils, a similar number to the temples, liver and ears. Two vessels are mentioned as reaching the

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bladder. A remedy for baldness consisting of donkey hoofs, dog claws, fats from animals, various oils and fruit juices were recommended.

Claude Bernard demonstrated the fat-splitting properties of pancreatic juice and stated gastric digestion only prepared the food for intestinal digestion. Eberle and Valentine before Bernard's discovery were convinced that the pancreatic juice was concerned with digestion although they believed the digestive phase was limited to the stomach.

The cherry-red color of the blood of animals following fatal administration of carbon monoxide was recognized by Claude Bernard.

During the sixteenth century, Benivieni described a tumor of the mesentery. The tumor probably was a dermoid cyst of the mesentery.

The term *tabes mesenterica* was coined in 1775 by Ball.

The term *lymphogranuloma inguinale* was named by Durnand Nicols and Favre in 1913. John Hunter described in 1786 the symptoms of such a disease.

In 1837, Rokitsansky first described volvulus of the cecum and ascending colon. Von Zege Mantucuffel intelligently discussed its mechanism in 1898.

Pawlowsky determined that if the bowel content was heated on eight

successive days and introduced into the peritoneal cavity peritonitis did not develop. He concluded that bacterin was the important factor in its production.

Aeromegaly was recognized as a distinct disease by Snucrotte in 1772. He described his patient as being 39 years of age and slightly over five feet in height. The lower jaw extended anteriorly beyond the upper maxilla a full inch. From the top of the teeth to the lower border of the chin was approximately four inches. Alibert, a dermatologist, described a similar case in 1822. Seven years later Mngendie makes mention of two women he had under observation with the same symptoms. It was not until 1864 that Vergn associated the pituitary gland with aeromegaly. Pierre Marie observed in Charot's clinic two patients suffering from aeromegaly. He, for the first time, separated the condition from Pngct's disease.

Nicholas Culpeper published in 1649 a text known as a *Physical Directory or a Translation of the London Dispensatory*. In this edition all the secret formulns contained in the *London Dispensatory* were exposed. At this time Culpeper was known as an astrologer and as a result he was a target for persecution by the medical profession. In 1653, he published a second text book mentioning over three hundred drugs made from English herbs which were not mentioned in any other books.

The progress in the treatment of gonorrhea was retarded for half a century because of the teachings of John Hunter, who persisted in adhering to the old tenets that gonorrhea and syphilis were different manifestations of the same disease. Hunter inoculated himself with pus from a patient suffering from gonorrhea. Within three months a syphilitic ulcer developed on his tonsils which proved to him and his followers that the two diseases represented a single entity. Ricard between the years 1831 and 1837 proved by repeated inoculations that gonorrhea and syphilis were separate and distinct diseases.

In 1837, Donne isolated the trichomonas from the vagina. He believed it to be the cause of gonorrhea. At a later date, he recognized the organism to be a normal inhabitant.

Neisser of Breslau identified the gonococcus in 1879, and in 1885 Brumm obtained a pure culture of these organisms.

Turner introduced copniba in 1729 and Crawford suggested the use of cubebs in 1818 in the treatment of gonorrhea.

Henderson and Panas recommended in 1865 the use of sandal wood oil as a remedy against gonorrhea.

A solution of silver nitrate as an irrigation treatment was suggested by Carmichael in 1818, and a solu-

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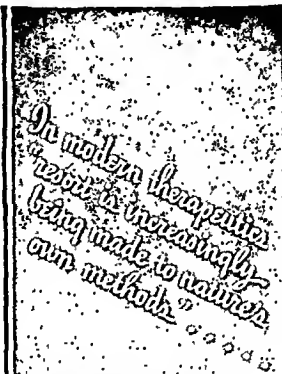
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Treatment, Wm. Wood & Co.
New York, 1921, p. 271.



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tion of potassium permanganate was recommended for the same purpose by Rich in 1864.

Stall, who lived 1742-1787, discovered that the prostate gland could be palpated through the rectum.

Celsus described a disease in which the output of urine was greater than the fluid intake and caused emaciation. Whether he was describing diabetes is not known. If so, he antedated Aretaeus who described and gave the disease its name.

Hippocrates was aware of trephining of the skull. He described an instrument for this purpose. He recommended that the instrument be placed in water at intervals to prevent overheating. Trepaning was not limited to fractures of the skull. Hippocrates used it to relieve failing vision when due to increase in intracranial pressure and Celsus advised it in meningeal hemorrhage.

The wire saw was introduced by Leonardo Gigli of Florence, in 1894.

Herophilus of Alexandria in 330 B. C. recognized the synchronous relationship between the heart and radial artery.

Stephen Hales, an English clergyman, published in 1733 his observations on blood pressure. He experimented on animals for a period of twenty-five years before reporting his results. His instrument consisted of a small brass pipe, one end of which was inserted into an artery. To the other end of the tubing a glass tube was attached. The tubing was held in a perpendicular position. The height the blood reached in the tubing was recorded in inches. No further efforts were recorded in an attempt to improve the instrument until Poiseuille, a French Medical student substituted mercury in the glass tubing in 1829.

The papyrus of Ebers written about 1600 B.C. mentions inflammation of the urethra and remedies used; however, it is questionable whether the Egyptians recognized gonorrhea.

The Biblical Jews knew that a urethral discharge resulted from coition.

Hippocrates, who lived 460-370 B. C., recognized five types of leucorrhea. A urethral discharge was thought to be due to ulcerating tumors in the urethra.

Galen, who lived 131-201 A.D., coined the term *gonorrhoea* which is derived from *gonus* meaning seed and *rhoea* meaning flow. He believed the discharge to be an involuntary control of the semen.

The endoscope was discovered by Descroix in 1865.

Theden, who lived 1714-1795, perfected an elastic urethral bougie.

Aretaeus, who lived during the second and third century A.D., recognized gonorrhoea in both sexes. He associated the disease with inactivity, feebleness, spiritlessness and a precursor of paralysis. He believed potent semen makes strong men and

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stimulates the growth of hair over the body. If the virility of the semen be lost, the body becomes emaciated, the voice assumes a sharp tone, the hair on the body and face disappears. He used this argument because such symptoms were present in eunuchs.

Cowper, who lived 1666-1709, described the glands which bear his name.

Rhazes, who lived 860-932, and Avicenna, who lived 980-1037, recognized the difference between a specific urethritis and seminal fluid. They described the gonorrheal discharge as being similar to barley dough dissolved in water and was the result of some internal disease.

Morgagni recognized the depressions of the urethra known as the lacunae of Morgagni. Terraneus and Cocburn independently and unknowingly to each other or to Morgagni described these lacunae.

The cecum of sheep was first used as a protective sheath against venereal disease. It was suggested by Dr. Conton, an Englishman. He was so severely criticized that he changed his name to Cundum from which the word condom arose.

Diabetes, derived its origin from the work siphon. The name was coined by Anetaeus, a Cappadocian who lived during the time of Galen and Celsus.

The use of powdered granite blown into the eye for corneal opacity is mentioned in the Ebers papyrus, a document written in 1552 B.C. The author of the papyrus of Ebers is not known. It was found between the thigh of a mummy in Thebes circa, 1858. The papyrus was purchased by Ebers from an Egyptian in 1872. It ultimately became known as the papyrus of Ebers.

Hippocrates stated that depressed fractures of the skull were not always dangerous unless the membrane was ruptured.

Bennett, who originally described the Bennett type of fracture of the thumb, also recognized in 1865 the sinuses of Morgagni. He discovered this anomaly while dissecting a cadaver at Trinity College. It was reported in the Dublin Quarterly Journal of Medical Science in 1865.

Silicosis was described by Ramazzini in 1700. Lanza and Higgins were probably the first in America to investigate the subject among coal miners.

In 1872, Burdon Sanderson described inflammation as "a result of injury, provided that the injury be not so excessive as to destroy the vitality of the part."

According to Matthew, diverticulosis of the sigmoid was described in Baillie's Morbid Anatomy, published in 1794.

Aberrant thyroid tissue was recognized by von Haller in 1779. In 1850, Stanley, an English surgeon, extirpated an aberrant thyroid gland.

In 1878, Martin popularized nephrectomy for the relief of a movable kidney.

In 1858, Santopadre performed the first cholelithotomy.

Pancreatic lithiasis was first described by Graaf in 1607.

In 1848, Geor B. Payne autopsied an individual dying from eclampsia. He stated that "it is extremely probable that the serous and cellular structures within the encephalon were also subject to this passive dropsy; the effusion, however, was not sufficient in amount to give indications of cerebral pressure, until congestion of the cerebral vessels under the parturient efforts increased the latent pressure so much as to excite the convulsive action."

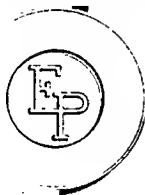
H. L. Dodge, writing in 1864, stated that puerperal convulsions arise from congestion of the blood vessels of the brain or from actual effusions of serum or blood into its substance or cavities.

Hahn conceived the idea in 1881 of fixing the kidney by sewing the perirenal fat to the walls of the lumbar incision by suture.

Arcaeus, who lived 1493-1573, refers to cancer of the male breast and

depletion

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states that it is not so frequent as cancer in females. Hildannus, who lived 1537-1619, describes such a case. Heister in his inaugural dissertation described male mammary cancer. Hortaloup in 1872 and Poirier in 1883 were the first to offer a systematic study of cancer of the male breast.

The Rammstedt operation for congenital pyloric stenosis was successfully carried out by Rammstedt in 1912.

Ried, a German surgeon, was first to recognize and report tuberculosis of the flat bones of the skull. He recognized two cases of tuberculosis of the skull. He used the term, perforating tuberculosis of the vault of the skull.

Petit performed the first cholecystostomy through adhesions which he had artificially created.

In 1876, Bobbs accidentally performed the first cholecystotomy. The enlarged gall bladder was mistaken for an ovarian cyst.

The differential blood count in common usage was described by Ehrlich in 1891.

The Edinburg Medical and Surgical Journal printed in 1814 gives a description of Colles fracture. The article was prepared by Abraham Colles and in less than sixteen hundred words concisely described this type of fracture. It is recorded that Colles collected less than five hundred dollars during his first year of practice in Dublin.

Dominick Corrigan at the age of thirty described the inadequacy of the aortic valves and the water hammer pulse.

John Cheyne's description of a peculiar type of breathing appeared in the Dublin Hospital Report in 1818. Stokes, in 1846, discussed the etiology and gave a more comprehensive description of the respiratory phase. It came to be known as the Cheyne-Stokes syndrome. Hippocrates described the same type of respiration.

In the year 1896, Murphy performed the first end-to-end suture of a divided artery.

LIUM, ROLF AND PORTER, JOSEPH.

Etiology of Ulcerative Colitis.
Arch. Int. Med., Vol. 63, pp. 201-225, Feb., 1939.

Colonic explants on to the abdominal wall were made in dogs. The mucosa remained essentially normal if protected by dressings. Any slight trauma would produce spasm in the explant and increase in secretion of mucus. After the graft was well healed it was possible to establish normal measurements, and measure the contraction produced by different stimuli.

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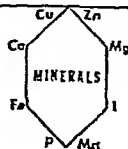
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1. Allen, A. M.—*Medical Record*, April, 19, 1939.

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acetyl choline and prostigmine would produce the same result, that is muscle spasm in the explant, secretion of mucus followed by a thin watery secretion, in turn followed by ulceration. Injection with Shiga toxin produced the same effect but in only part of the dogs.

The authors suggest that ulcerative colitis may be due to spasm of the muscle of the bowel due to a variety of causes.

K. W. Benson.

BARRON, EDGAR.

Aspiration for Removal of Biopsy Material from the Liver. Arch. Int. Med., Vol. 63, pp. 276-289, Feb., 1939.

Aspiration was done with a thirteen gauge needle nine centimeters in length. The point of the needle was inserted just below the costal margin to the right of the xyphoid, pointing to the lower portion of the right axilla. In view of the dull visceral pain produced a strong hypnotic was used as well as a local anesthesia.

In thirty-five consecutive cases of hepatomegaly a positive diagnosis was established by this method. Repeated punctures were sometimes necessary. Though there were no complications in this series, in one subsequent case death resulted from hemorrhage.

Comment: It is a step forward to be able to establish the nature of hepatomegaly without laparotomy. This is especially true because in most liver disease nothing more than diagnosis can be accomplished surgically.

Peritoneoscopy is a more elaborate procedure but it offers advantages over blind puncture. Biopsy may be made under direct vision, and hemostasis is possible.

K. W. Benson.

SCHINDLER, RUDOLF AND SIRBY, A. M.

Gastroscopic Observations in Pernicious Anemia. Arch. Int. Med., Vol. 63, pp. 334-355, 1939.

Change in the gastric mucosa in pernicious anemia was first noted in 1860. It was once agreed that the fundamental change was atrophy of the gastric mucosa, most pronounced in the cardia. In recent years there has been much disagreement as to the findings, particularly among gastroscopists.

This paper is based in the gastroscopic observation of twenty-three patients with undoubted pernicious anemia.

Nine untreated patients presented superficial gastritis, atrophic gastritis, or both. None were normal.

Atrophic changes were found throughout the stomach or in the body alone, in some cases the antrum was free.

Cases receiving adequate liver therapy would have a normal mucosa, there might be no change resulting from liver, or the atrophy might progress.

The authors suggest that there must be two separate diseases of the stomach in pernicious anemia, a primary dysfunction of the "anti-anemic" cells, and a secondary degeneration of the surface epithelium with superimposed inflammation.

K. W. Benson.

BUTT, HUGH R., SNELL, ALBERT M. AND KEYS, ANCEL.

Plasma Protein in Hepatic Disease. A Study of the Colloid Osmotic Pressure of Blood Serum and Ascitic Fluid in Various Diseases of the Liver. Arch. Int. Med., Vol. 63, pp. 143-155, Jan., 1939.

It has been known for more than thirty years that there is change in the serum protein in hepatic disease. This change is a reduction of total protein and particularly in the serum albumen. This is most probably due to failure of production of protein in the liver, but might be of nutritional origin, or less likely because of loss of serum albumen into ascitic and edema fluid because of increased capillary permeability.

In this study total protein, albumen and globulin are determined and compared with the colloid osmotic pressure done by the membrane bag method of Starling.

Determinations were made in twenty-three cases of subacute and chronic atrophy of the liver with nodular regeneration (cirrhosis). Nineteen had ascites or edema. In twenty-two the colloid osmotic pressure was low though in only seven was the serum protein less than six grams per one hundred cubic centimeters. There was a better correlation between serum albumen and colloid osmotic pressure. Colloid osmotic pressure varied roughly according to the degree of liver damage as revealed by functional tests.

Colloid osmotic pressure studies should be of value in clinical studies of edema and ascites.

K. W. Benson.

FALCONER, M. A. AND LYALL, A.

Treatment of Uremic Intoxication Complicating Pyloric Stenosis with Vomiting. Australia and New Zealand J. of Surg., 8, 37, 1938.

Prolonged vomiting associated with pyloric stenosis may lead to uremic intoxication, a term preferred by the authors to alkalosis. Clinically, the picture resembles uremia as seen in primary renal insufficiency, ranging from headache, nervous irritability

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2. Q. How is weaning done gradually?

A. One bottle replaces a nursing at 6:00 P. M. the first week; two bottles at 2:00 and 6:00 P.M. the second week; three bottles at 10:00 A.M., 2:00 and 6:00 P.M. for the third week, etc.

3. Q. What is the total formula for twenty-four hours for weaning?

A. Milk, whole, 24 ozs. Boiled water, 8 ozs. Karo Syrup, 3 tablespoons. Four feedings, eight ozs. every four hours.

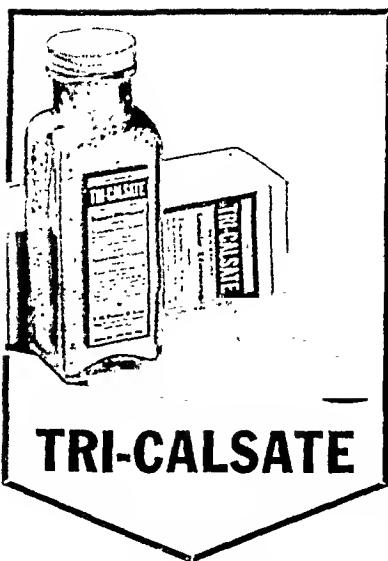


Infants should be weaned from the breast at about eight months. The season of the year is immaterial with modern knowledge of nutrition and hygiene. Gradual weaning is accomplished by progressively increasing the number of bottle feedings in substitution for the breast feedings.

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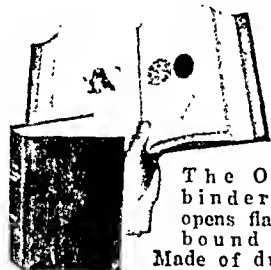
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and dehydration in mild cases, to incoherence, coma, twitching and tetany in the severe types. Laboratory findings may show albuminuria and acetonuria, usually alkaline urine, increased blood urea and Co. combining-power, decreased plasma Cl, polycythemia, diminished urinary chloride, low urea concentrating power of the kidneys. Toxic symptoms are due to salt-water loss from the body, which upsets the normal fluid balance and results in fatal changes in the physicochemical equilibrium of blood and tissues, unless inorganic electrolytes are replaced.

Alkalis aggravate the symptoms and biochemical changes, and are therefore contraindicated. The blood urea level is the most significant and reliable criterion and should be estimated before every operation, being more important than the chloride level. If the toxemia from persistent vomiting is not corrected, as shown by the absence of azotemia, surgery may result fatally.

Treatment is directed towards correction of dehydration and starvation of body tissues, gastric retention, azotemia, hypochloremia, alkalosis and tetany. In addition to the use of frequent liquid or semi-solid feeding, gastric lavage, belladonna, adequate fluids by elysis or infusion, etc., and avoidance of alkalis it may be necessary to do a jejunostomy and to continue jejunal feeding in refractory cases until the chemical status is restored to normal before going ahead with further surgery. In replacing the NaCl loss, one must avoid an excess as this may lead to edema. The authors report 2 cases successfully treated by jejunostomy.

Albert Cornell, New York, N. Y.

PARTURIER-LANEGRACE, M.

Ulcères et grossesses. Arch. d. ma. de l'app. digestif., 26:1092, 1936.

Parturier-LaneGrace's case histories suggest that pregnancy has a favorable effect on the course of peptic ulcer, which is in line with the views of Sandweiss in this country.

Walter C. Alvarez, Rochester.

FORTY, FRANK.

Intestinal Atresia with Torsion of Meckel's Diverticulum. Lancet, vol. 236, p. 986, April 29, 1939.

Congenital obstruction of the newborn is of two varieties. One condition is the so-called septate ileum where the continuity of the intestinal lumen is interrupted at one or more points by septa covered on both sides by mucous membrane. The other is where the bowel is divided into two main segments and the two segments are connected with each other only by an impervious fibrous coat of vary-

ing length. The obliteration of the intestinal lumen is probably due to disturbances of the normal embryological processes involved in closing of the vitello-intestinal duct.

M. H. F. Friedman, Detroit, Mich.

PAUL, MILROY.

Enteric Intussusception Due to Invagination of Meckel's Diverticulum. Brit. Med. J., p. 504, March 11, 1939.

An intussusception by invagination of Meckel's diverticulum is rare indeed. Referring to the paper by Harkins (Ann. Surg., v. 98, p. 1070, 1933), Meckel's diverticulum was found in only 1.3 per cent of twenty-five thousand autopsy cases. In all intussusception condition, Meckel's diverticulum was the causative agency in 2.5 per cent of the cases; the age incidence was greatest in the first two decades and more than three-quarters of the cases were males.

M. H. F. Friedman, Detroit, Mich.

BENNETT, T. I. AND GILL, A. M.

Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer. Lancet, p. 500, March 4, 1939.

Some thirty patients of both sexes, ages 29 to 72 years, with gastric, duodenal and anastomatic ulcers of 3 months to 40 years duration were treated with aluminum hydroxide gel. It was found that the gastric contents were effectively neutralized and that the aluminum hydroxide did not cause alkalosis. In all but one case diarrhea was absent.

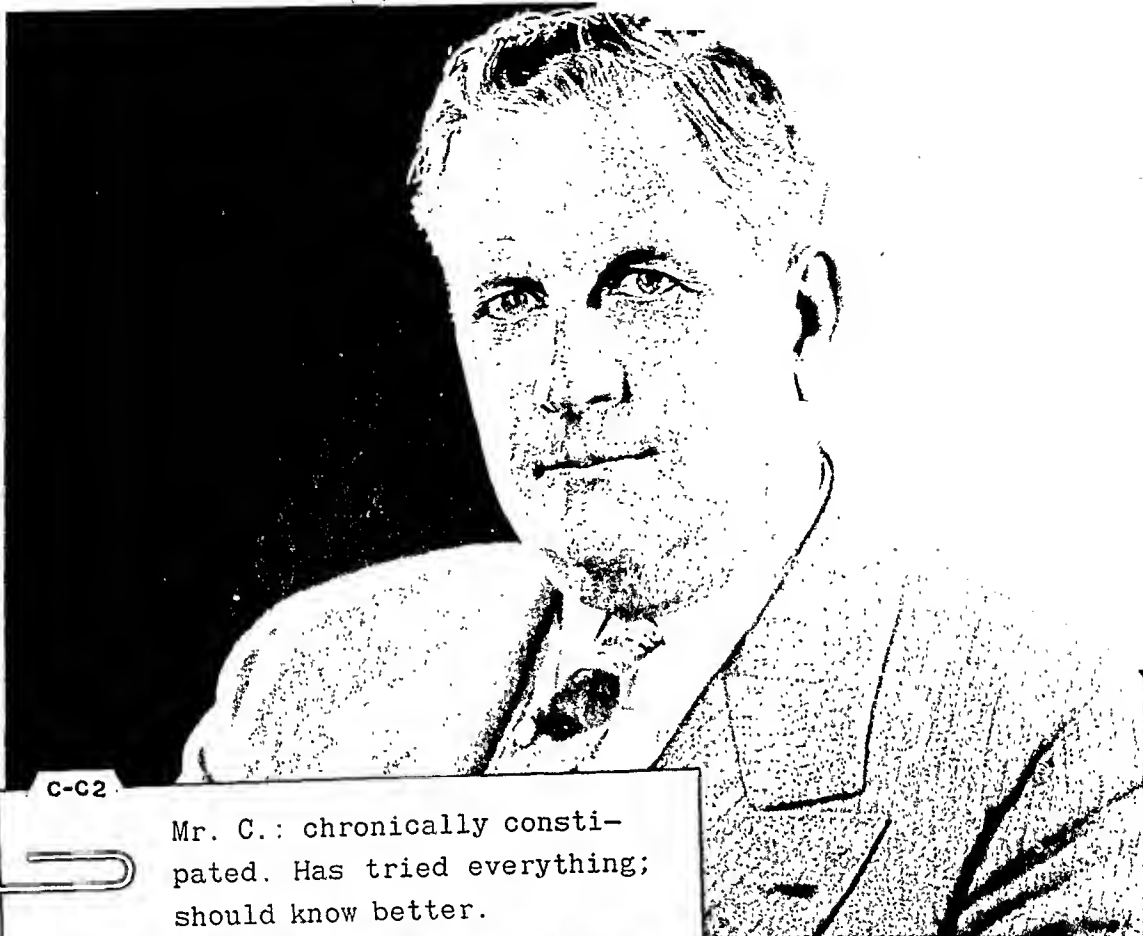
M. H. F. Friedman, Detroit, Mich.

SUSMAN, M. P.

Perforation of the Stomach and Duodenum Due to Simple Ulcer and Carcinoma. Med. J. Australia, 26th year, No. 12, p. 456, March 25, 1939.

An analysis of 83 cases of peptic ulcer patients in the author's practice in both London and Australia is made. The mortality rate for perforated gastric ulcer was much higher than for perforated duodenal ulcer (58.8% as compared with 19%). All of 63 patients with duodenal ulcer were males and Susman says that he has yet to see a female with proven duodenal ulcer. Gastro-enterostomy should be performed at the time of simple closure of the perforation only if the patient's condition is good and if the ulcer is chronic or there is evidence of pyloric stenosis. Perforation of gastric carcinoma is rarer than that of peptic ulcer. The patient may survive the perforation (if attended to early) but the incidence of recurrence and extension of the growth is high.

M. H. F. Friedman, Detroit, Mich.



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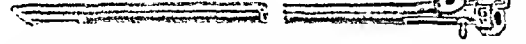


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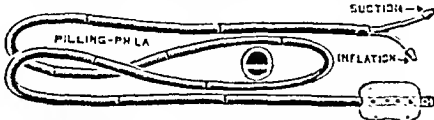
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Chemical and biological investigations have demonstrated that different proteins may vary widely in both chemical composition (2) and ability to satisfy the nitrogen requirements (1, 3) of various animals. Of the twenty-odd amino acids which have been isolated from proteins (4) arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine have been shown to be essential in mammalian nutrition. The biological value of a protein is in reality a measure of its ability to supply those amino acids essential for tissue building and repair which the animal cannot synthesize (5) from material "ordinarily available" at a rate sufficient to meet body demands. A "complete" protein is one which will supply—or at least contains—the essential amino acids. Few proteins approach this ideal condition. Fortunately, however, a varied diet, containing proteins of both vegetable and animal origin, will usually supply all the essential amino acids which may not be supplied in adequate amounts by any one of the proteins.

As to the amounts of protein needed by men, experiments of the balance sheet or endogenous nitrogen elimination types (3, 6) have demonstrated that the protein require-

ments of the human adult may apparently be adequately met by relatively low protein intakes. These intakes are of the order of 0.5 gram per day per kilogram of body weight. However, there is evidence (3) that development of physique and general health is favored by more liberal protein intake. Since excess of protein above the requirement for tissue repair and growth is utilized as a source of fuel, the present trend is toward more liberal protein allowances.

In infancy and childhood, suggested protein allowances (3) are relatively high, being of the order of 3 to 4 grams of protein per kilogram of body weight in infancy and gradually decreasing with increasing age until adult allowances (3, 6) of 0.75 to 1.5 grams protein per kilogram of body weight are reached. Protein allowances of the order of 10 to 15 per cent of total calories as protein calories in the mixed diet throughout the entire life cycle, appear to be satisfactory. In the formulating of a mixed diet calculated to supply optimal amounts of proteins, the canned meats, marine, dairy and vegetable products may be freely used.

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(3) 1937 Nutrition Abstracts and Reviews, 7, 257

- (4) 1937. J. Am. Med. Assn. 109, 2070.
(5) 1938 Annual Review Biochemistry, 7, 356
(6) 1938. J. Am. Med. Assn. 111, 1111, Fifth Edition, C. C. Van Nostrand Company, Inc., New York

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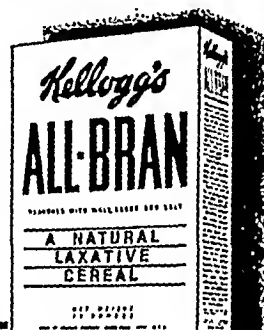
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The Absorption of Hydrochloric Acid by the Human Stomach*

By

HARRY SHAY, M.D., J. GERSHON-COHEN, M.D., D.Sci. (Med.)

and

SAMUEL S. FELS, LL.D.

NEW YORK, NEW YORK

SEVERAL years ago while studying the problem of duodenal regurgitation in man in relation to the control of gastric acidity, we (1) used in some of the experiments a hydrochloric acid gastric meal. We were impressed by the rapidity with which the acidity of the test meal decreased. Believing then that the rapid changes observed were due neither to dilution nor to neutralization, we wondered whether they might not represent an absorption of hydrochloric acid by the stomach. To the acid meal we added various indicator substances which we hoped would not be adsorbed or absorbed by the stomach mucosa, and attempted, at that time, to study this mechanism further. Unfortunately, we were unable to find an indicator that was suitable and were forced to leave our suspicion without experimental support.

In 1933, Teorell (2) advanced a modified version of the mechanism suggested by us. From studies in the cat, he believed that hydrochloric acid diffused out of the stomach, through the mucosal wall, while neutral chloride passed into the gastric cavity. He believed that there normally exists across the gastric mucosa an exchange of hydrogen-ion from the gastric juice and sodium-ion from the tissue fluid or blood. Latterly, Wilhelmj, O'Brien and Hill (3), studying secretion in whole stomach pouches in dogs did not find support for an acid absorption mechanism.

In a recent splendid survey of the factors which reduce gastric acidity, Hollander (4) questions the likelihood of HCl absorption. This on the basis that such a process could in no way account for the low acid values at the beginning of secretion although he does admit that it may explain the post maximal drop in acidity.

In fundic pouches in dogs in which the secretion was retained for considerable periods by means of a sphincter action on the mouth of the pouch, Hollander failed to find a significant diminution in acidity. While these experiments supplied definite evidence that acid was not absorbed by fundic pouches, Hollander recognized the possibility that other parts of the gastric mucosa might do so. The question of gastric absorption of acid remained incompletely answered.

In 1934, we (5) showed that adequate duodenal stimulation in man may close the pylorus completely and thus stop gastric evacuation for variable periods. This method, coupled with the introduction of one suitable to the determination of phenol red in gastric contents by Hollander, Penner and Saltzman (6), prompted us to reexamine the question of the gastric absorption of hydrochloric acid. While phenol red was studied by Hollander, et al, as a dilution indicator and as such possessed most of the ideal requisite character-

istics as first suggested by Gorham (7), we employed it rather as a measure of pyloric closure, recovering 100% of the ingested dye from the stomach at the end of the test period. That phenol red may be so employed is supported by the recent work of Penner, Hollander and Saltzman (8) who reported that this dye is not absorbed from the human stomach, is not altered chemically by its contact with the gastric secretions, and does not preferentially stain the mucous membrane to a significant degree. Our own experiments in which we have used phenol red as an indicator fully confirm their results. The principle of the method of phenol red determination of Hollander and his associates consists briefly in centrifugation of the recovered gastric specimen, alkalization with CaO, treatment with NaOH and Zn SO₄ to precipitate proteins and bile, centrifugation, and treatment of the supernatant fluid with Na₃ PO₄ to remove excess Zn and to adjust the pH to about 11-12, a value at which the phenol red is entirely on the alkaline side. Comparison is then made with a standard phenol red solution. We found that colorimetric comparison was simplified by introducing a green filter Wratten 74.

EXPERIMENTAL METHOD

Patients without gastric complaints who showed anatomically normal stomachs by X-ray were selected. Two groups were chosen, those with a normal gastric secretory response to the Ewald meal and others who were anacid with such a meal. These were thoroughly tube-broken by several intubations before the studies were undertaken. After an overnight fast, the stomach was intubated with two tubes. One was passed into the duodenum in the usual manner while the other remained in the stomach. Olive oil was instilled through the duodenal tube at the rate of 50 drops per minute. The stomach was then completely emptied in all positions of its fasting contents through the gastric tube. Through this tube was then instilled 200 cc. of a solution of approximately 0.5% or 1% HCl in distilled water containing 2 mgms. of phenol red per 100 cc. Thirty minutes after the gastric instillation, the stomach was emptied completely in all positions through the gastric tube. The stomach was then lavaged twice with 200 cc. portions of distilled water and emptied completely after each lavage.

A portion of the test meal, the recovered gastric contents, and all the washes were examined for pH with a Beckman pH meter; for total chlorides by the Wilson and Ball (9) method, and for phenol red as indicated above. To read very dilute solutions of the phenol red, we found useful the application suggested by Wilhelmj (10); namely, adding the unknown to a portion of the standard solution and reading against

*From the Medical Research Laboratory, Samuel S. Fels Fund and the Gastro-Intestinal Division, Medical Service 1, Mt. Sinai Hospital. Submitted April 1, 1939.

TABLE I

Specimen	Vol. cc.	Free Acid mEq./l	Total Acid mEq.	pH	Conc. Chloride mEq./l	Total Chloride mEq.	Conc. Dye mgm./100 cc.	Total Dye mgm.
Test Meal	200	133.1	13.31	0.95	133.1	26.62	2.00	4.00
Recovered Meal	270	110	12.0	1.00	128.7	29.60	1.63	3.74
First Wash	200	0	0	5.64	0	0	0	0
Recovered First Wash	210	not done	not done	2.22	10.7	2.25	0.11	0.23
Second Wash	200	0	0	5.64	0	0	0	0
Recovered Second Wash	205	not done	not done	3.01	3.5	0.72	0.04	0.08

SUMMARY

Total Chloride Test Meal	26.62 mEq.
Total Chloride Recovered	32.57 mEq.
Total Chloride Added by Stomach	5.95 mEq.
Percentage Increase Total Chloride	23%
Chloride Concentration Fasting Gastric Contents	81.7 mEq/l.

Not only did absorption not occur with this concentration of acid 133.1 mEq./l. (0.48%) but actual secretion must have occurred because of the increase in chloride recovered. This increase could not represent fasting contents left behind because it would have required 73 cc. of the fasting contents to have supplied the additional chloride.

Total Dye Test Meal	4.00 mgms.
Total Dye Recovered	4.05 mgms.
Difference	0.05 mgms.
Error	1.3%

If we consider the steps involved both in recovery of the samples and the determination of the dye in each sample, the above is a very acceptable experimental error.

a similarly diluted standard. Titration of free acid was done in the usual manner.

We have repeatedly obtained results in both normal acid and anacid patients as illustrated in Tables I and II.

DISCUSSION

Our data show that hydrochloric acid concentrations of approximately 0.5% or 1% are not absorbed by the human stomach when left in contact for periods up to 30 minutes. Considering the speed of concentrated glucose absorption by the stomach (11) in the same period of time, we believe the trial period adequate.

Our data indicate also the acidity required to inhibit gastric secretion completely. There is a concept that the introduction of approximately 0.1 normal (0.36%) solution of hydrochloric acid into the stomach will always completely inhibit the secretion of acid chloride during a thirty minute test period. This has not been confirmed by the work of Apperly and Norris (12) or of Wilhelmj, O'Brien and Hill (13). More recently, Welch and Comfort (14) found that following such a test meal, hydrochloric acid was definitely secreted in 65% of their cases and was probably secreted even in a great majority of their remaining cases. Our own experiments show that test meals of concentration as

TABLE II

Specimen	Vol. cc.	Free Acid mEq./l	Total Acid mEq.	pH	Conc. Chloride mEq./l	Total Chloride mEq.	Conc. Dye mgm./100 cc.	Total Dye mgm.
Test Meal	200	275.3	27.53	0.68	275.3	55.06	2.00	4.00
Recovered Meal	225	210	23.2	0.76	232.3	52.30	1.66	3.74
First Wash	200	0	0	5.72	0	0	0	0
Recovered First Wash	205	not done	not done	2.11	11.6	2.38	0.07	0.14
Second Wash	200	0	0	5.72	0	0	0	0
Recovered Second Wash	205	not done	not done	3.27	5.2	1.07	0.04	0.08

SUMMARY

high as 0.5% hydrochloric acid failed to prevent gastric secretion for a period of 30 minutes. In fourteen such experiments the recovery of chloride ranged from 15% to 23% above the total chloride content of the test meal. In 12 experiments in which approximately a 1% acid meal was used, gastric secretion was completely inhibited for the duration of the experiments.

SUMMARY

We were able to study the question of HCl absorption in man by inducing sufficient duodenal stimu-

lation to arrest gastric evacuation and by using phenol red as an indicator of that arrest. This was possible because phenol red in concentration of two milligrams per 100 cc. is not absorbed by the human stomach. Hydrochloric acid in concentrations of approximately 0.5% or 1% is not absorbed by the stomach when such solutions are in contact with it for periods up to 30 minutes. Hydrochloric acid meals of 0.5% concentration do not completely inhibit gastric secretion, while 1% meals do cause complete inhibition.

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Treatment of Peptic Ulcer With Colloidal Aluminum Hydroxide*

By

E. R. KYGER, JR., M.D., EDW. H. HASHINGER, M.D.

and

E. W. WILHELMY, M.D.

KANSAS CITY, KANSAS

IN the present series of cases we have attempted to evaluate clinically and radiographically the results of administration of a 10% colloidal aluminum hydroxide gel to a rather diversified group of ulcer patients, comprising sixty-two X-ray proved cases. Fifty-eight of these returned for follow-up study including additional X-ray studies in forty. The lesions were duodenal in fifty-six, gastric in four, and marginal in two. In the duodenal group the average duration was 6.88 years, in the gastric group 7.75 years, and in the marginal group 3.75 years. Eight of this series represent hemorrhage cases, four of which were treated by the continuous drip method. Two cases of the more severe type, one a penetrating duodenal ulcer, and the other a large penetrating gastric ulcer, were treated by the drip method described by Woldman and Rowland (2, 3, 4). Several patients with various degrees of obstruction were treated orally.

The preparation used was a 10% gelatinous mixture of colloidal aluminum hydroxide,† one volume of which is capable of neutralizing 24 to 25 volumes of tenth normal hydrochloric acid within thirty minutes. To ascertain as far as possible the effectiveness of the preparation, the ambulatory patients were instructed to take six meals daily from a list of simple bland foods, and no attention was given to other factors such

as rest or focal infection. The aluminum hydroxide gel was taken six times daily in 4 cc. doses between feedings. Those treated with the drip method were given from 500 to 1000 cc. of a 2% solution daily by a simple gravity drip. A soft latex tube was used in the latest of these cases and proved to add much to the patient's comfort. Although it is impossible to aspirate samples through this tube, the amount of aluminum hydroxide given is in excess of the theoretical requirement to neutralize all the acid in even the most severe cases of hypersecretion.

RESULTS

The results of this series are portrayed in Fig. 1. Complete radiographic healing occurred in 40% of the cases in the follow-up within an average of 98.7 days. Two of these patients relapsed two and three months following treatment. An additional group, comprising 22½% of the cases, showed such clinical and radiographic improvement that the remaining deformity of the bulb was felt to represent permanent scarring. The average period of healing in this group was 165 days. Three of these cases relapsed after three, twelve and fifteen months. Of the remaining cases 25% were improved radiographically after an average of 94.5 days treatment, and 12.5% showed no radiographic improvement in an average of 97.8 days. It is interesting that four patients who at first showed no X-ray improvement were in two instances later improved,

†Colloidal Aluminum Hydroxide Hydrogel-Breon furnished for this group of cases by the George A. Breon Company, Kansas City, Mo.
*From the Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, Kansas.
Submitted April 20, 1939.

and in the other two instances eventually healed completely by continued therapy. In all, eight cases of hemorrhage bleeding was promptly controlled regardless of the method of treatment. All of those treated by the drip method were relieved of pain within a few hours, and with one exception showed rapid X-ray improvement. Samples of the gastric contents were taken frequently and at no time was free acid found to be present in those treated by the drip.

Symptomatic relief was obtained by 89.2% of the entire series. Two or three days generally elapsed before those on the oral regime experienced complete relief. In four patients (7.2%) only partial relief was obtained. One patient with marked hypersecretion, controlled by the drip method, was unable to obtain

true in our ambulatory patients, possibly because of more liberal feeding or perhaps from smaller dosage. One patient took extra doses "for their laxative effect." The large amounts given by the drip method necessarily produce hard, bulky stools. We feel that one of the advantages of aluminum hydroxide over other antacids is the absence of the irritating action on the intestinal tract possessed by the magnesium compounds so frequently given in powders. A number of the patients complained that the initial doses of the gel were distasteful. In our experience this was the most striking untoward effect of the treatment. However, the patients soon became accustomed to the gel and took it readily when their pain was relieved—with two exceptions. These were previously mentioned as

Results of treatment

X-Ray (40 cases)					Clinical (55 cases)			
	Unimproved	Improved	Healed Scar	Entirely Healed	Unimproved	Partial Improved	Entirely Well	Recurrence
1 year or less	1	4	—	4	—	1	12	—
1 to 5 years	2	3	3	6	—	1	19	4
over 5 years	2	3	6	6	2	2	18	3
Total	5	10	9	16	2	4	49	7
Percentages	12.5	25.	22.5	40.	3.6	7.2	89.2	12.7

relief of nocturnal pain when put on the oral system. One patient refused to take the preparation because it gave him the "hiccups," and another refused it because of nausea. In addition, there were three patients who were excluded from the computation of these results because they failed to follow the outline of therapy.

COMMENT

The results of this series conform generally to those reported by others. We feel that the clinical and radiographic results of those managed by the relatively simple oral method are comparable to what might be expected from any well regulated Sippy regime in a similar group. We have no right to believe that this method of treatment will give more permanent results than any other form of antacid therapy. However, it is well adapted to prolonged use in cases that are slow to respond, and so far has been effective in promptly controlling the recurrences. One of the gratifying features of the treatment, mentioned by others and noted in this series, is the striking gain in weight made by many of the patients.

We have also been interested to observe the undesirable side effects of the treatment. Ivy (1) and others have mentioned the fact that a number of their patients were constipated. We did not find this to be

the ones who refused the preparation because of nausea and "hiccups."

CONCLUSIONS

(1) Colloidal aluminum hydroxide is effective in a simple ambulatory regime in producing symptomatic relief in almost every ordinary case of peptic ulcer and in promoting satisfactory radiographic improvement in most.

(2) The colloidal aluminum hydroxide drip is highly effective in controlling severe hemorrhage, in relieving the pain in severe cases, and in promoting rapid healing of the ulcer.

(3) The importance of etiological factors other than acidity is not minimized.

The very careful X-ray studies in this group were made by Dr. Galen Tice, roentgenologist-in-chief at the University of Kansas Hospitals.

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Note on the Value of Woldman's Phenolphthalein Test for Gastro-Intestinal Lesions*

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A SIMPLE test for determining the presence of gastro-intestinal lesions was recently described by Woldman (1). This test is based on the author's belief that the free phenolphthalein found in the urine of patients after the ingestion of a relatively small amount of the substance, appears in the urine because it has passed freely through an area denuded of mucous membrane, such as occurs for instance in peptic ulcer.

Because of the simplicity of the test and its obvious clinical value (if the claims of Woldman could be substantiated) it was employed in a series of cases. The method described by Woldman was accurately followed. A dose of 0.1 Gm. of white phenolphthalein dissolved in 10 cc. 95% alcohol and diluted to 30 cc. with water, was administered to the subject of the test on a fasting stomach. No food or drink was taken for another hour. Specimens of the urine were obtained two and four hours later, and in cases of acute and chronic nephritis, cardiac failure, fever and dehydration also at six hours. The presence of free phenolphthalein was determined by the addition of 10% sodium hydrate in the usual manner.

A total of 105 unselected cases were included in this investigation. Except for 12 prenatal cases from the Outpatient Department, they were ward patients and represented a cross-section of a general hospital population.

Rather early in the investigation doubt was thrown on the accuracy of the test since its repetition in individual cases was not productive of constant results, gradations from negative to strongly positive being observed in the same cases in tests performed at appropriate intervals.

The highest proportion of positives was obtained in the groups listed as (a) "Metabolic diseases" (3 cases of Diabetes Mellitus and 2 of Hyperthyroidism), and (b) "Extra-G.I. Tract Tumors" (including Hypernephroma, Lymphosarcoma of Abdominal Lymph Nodes and Giant Follicular Hyperplasia of Brill), namely 80%. The next highest proportion occurred in the group of active gastro-intestinal lesions, i.e. 69%. In this group of thirteen cases, four, or over 30%, gave negative results in tests repeated several times for confirmation. One of this group of four came to laparotomy at which advanced carcinoma of the stomach with extensive ulceration was found. The strongest positive reactions were obtained in a case of Giant Follicular Hyperplasia of Brill; at autopsy no break in the mucous membrane could anywhere be found. If the prenatal group, which may be considered

essentially normal, and the group consisting of active gastro-intestinal lesions are excluded, the test is found to be positive in 46% of the cases.

The high percentage of positive results may in part be accounted for by the fact that rhubarb, senna and cascara, in addition to certain other cathartics as well as phenolphthalein, impart a brown color to the urine which changes to red on addition of alkalis. Furthermore, uro-rosein and uro-erythrin likewise impart a red color to an alkaline urine (2). It was, however, not considered worth while continuing with a variation of the test designed to eliminate uro-rosein and uro-

Results of Woldman test in group of 105 cases

Disease Group	No. of Cases	Pos. W. Test	Neg. W. Test
Prenatal cases	12	1 (8.3%)	11
Cardiovascular	13	5 (38.4%)	8
Ulcer and Ca. Stom. and Int.	13	9 (69 %)	4
Other G.I. diseases	17	6 (35.3%)	11
Minor surgery and Orthopaedic	19	7 (37 %)	12
Metabolic diseases	5	4 (80 %)	1
Gynecological diseases	6	2 (33.3%)	4
Pulmonary diseases	3	1 (33.3%)	2
Extra-G.I. Tract tumors	5	4 (80 %)	1
Miscellaneous	12	4 (33.3%)	8
	105	43 (40.9%)	62

erythrin and to control the intake of substances likely to interfere with the accuracy of the test, because of the high proportion of negative results obtained in cases with active gastro-intestinal lesions.

CONCLUSIONS

1. In a series of 105 cases representing a wide range of diseases, including those of the gastro-intestinal tract, a large proportion gave a positive Woldman test, i.e. over 40%. An even higher percentage is obtained (46%) if the groups consisting of gastro-intestinal lesions and the prenatal cases, totaling 25 cases, are excluded. These figures are entirely out of the realm of probability as representing the percentage of ulcerative gastro-intestinal lesions in an unselected group of cases in a general hospital.

2. In a number of cases in which the test was re-

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peated several times at appropriate intervals, the results were inconstant, varying from negative to strongly positive.

3. Some of the cases giving the strongest reactions had no gastro-intestinal lesions; one such case came to autopsy.

4. In the group of cases representing active gastro-intestinal lesions, over 30% gave negative results.

5. This test does not take into consideration

certain substances other than phenolphthalein which give a red color in alkaline urine.

6. The Woldman phenolphthalein test does not constitute a test for the presence of gastro-intestinal lesions.

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The Use of Secretin as a Clinical Test of Pancreatic Function*

By

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THE study of pure pancreatic juice has hitherto been possible only when the secretion was obtained in the experimental animal through a fistula in the pancreatic duct, or occasionally in man in accidental post-operative pancreatic fistulas. All the earlier physiologic studies of the secretion of the gland by Claude Bernard, Bayliss and Starling, and Pavlov were made by introducing a cannula into the pancreatic duct.

In recent years McClure (1) and Myers (2) in this country and Christiansen (3) in Denmark have carried on many clinical investigations in man. They studied the duodenal juices obtained through the tube and attempted to evaluate pancreatic activity by studies of enzyme concentration. Pancreatic stimulation was induced by the administration of various single foods and admixture of foods introduced either into the stomach or intra-duodenally. Studies were made at different periods of digestion from samples of duodenal juice. Inorganic substances such as water, hydrochloric acid, magnesium sulphate were also used as pancreatic stimulants.

While these studies have afforded a valuable insight into the enzyme response to the various food stimuli, it became apparent that the failure to obtain pure uncontaminated pancreatic juice gave rise to variable results. The admixture of the acid chyme from the stomach, or the discharge of hydrochloric acid into the duodenum even in the fasting state lowers the pH of the duodenal juices by neutralizing the bicarbonate and inhibits the optimum enzyme activity. These variable and inconstant results have rendered unreliable the routine application of the clinical enzyme studies. Only as recent as 1934 a report by a committee of the American Gastro-Enterological Association on "A Survey of Enzyme Test" (4) revealed that only twenty-seven of its one hundred thirty-five members performed tests for one or more of the pancreatic enzymes.

Since Bayliss and Starling in 1902 discovered the presence of secretin in the intestinal mucous membrane and described its specific effect upon the external secretory cells of the pancreas, many attempts

have been made to isolate the hormone and utilize it experimentally and clinically. Chiray, Salmon and Mercier (5) in 1926 used a secretin prepared according to a method by Pinan and Simonet. In 1934 extensive studies were carried on in animal and man by Voegtlin, Greengard and Ivy (6), using a secretin prepared by Ivy. They obtained a definite increase in the output of pancreatic juice and enzymes after the intravenous administration of secretin. In their series of twenty-two cases they felt, however, that the results were of little clinical value, especially when a systemic reaction occurred following a repeated injection. (Ivy has since reported the preparation of a crystalline secretin (7)). It remained for the Swedish investigators, Hammarsten, Agren and Wilander (8, 9) to prepare secretin in a pure state. They have studied extensively its physiological and pharmacological properties in the cat and standardized it in units. Hammarsten, Agren, Lagerlof and Berglund (10, 11, 12) also carried on these studies in man and have reported a series of important clinical observations. They also attempted to establish the normal limits of the response to secretin per given time and body weight. Utilizing the double tube method in collecting the secretion according to Lim, Matheson and Schlapp (13) they were able to obtain an uncontaminated pancreatic juice without interference of the gastric hydrochloric acid stimulus. Also by this method they were able to study for the first time clinically the bicarbonate content of pancreatic juice in man.

Secretin* is an extract prepared from the small intestines of the hog. It is a whitish powder, readily soluble in water, stable in character and not affected by boiling. It is a non-toxic, antigen-free substance. It has no effect upon the blood pressure and aside from an occasional, slight and temporary flushing of the face it produces no untoward effects.

The present report is based upon the study of twenty-two cases consisting of fourteen normal individuals who had no gastro-intestinal disturbances or any biliary or pancreatic disorders, and eight abnormal cases. We have studied and tabulated the physiological response in the normal state. We have

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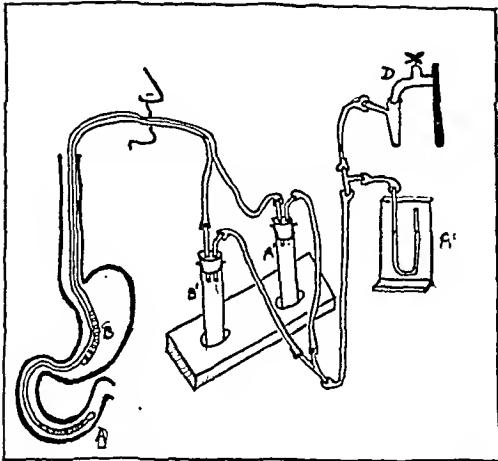


FIG. 1: DOUBLE TUBE AND SUCTION APPARATUS INSTALLED

also noted the variations in the response in the pathological states and their diagnostic significance.

NORMAL PANCREATIC RESPONSE TO SECRETIN

The effect of secretin, when injected intravenously, is to produce a marked increase in the flow of pancreatic juice which is rich in bicarbonate and enzymes. This increased output lasts about one and a half to two hours, and the effect may be repeated if at the end of this period a second injection of secretin is given.

The normal response of the gland is to be evaluated by quantitatively estimating the following factors:

1. Volume of flow
2. Concentration of bicarbonate
3. Concentration and quantity of enzymes: diastase, trypsin and lipase.

TECHNIC

The following procedure is employed in carrying out the secretin test. A special double gastro-duodenal tube* is used which permits the separate collection of gastric and duodenal contents by preventing the admixture of the two secretions and assures the collection of pure duodenal juice. The lower ten inches of the tube is a single channel which enters the duodenum, whereas the upper part is a double channel tube which remains in the stomach. The tube is introduced under the guidance of the fluoroscope and the tip is rapidly advanced to the pylorus avoiding coiling in the cardia. The patient is then allowed to lie on the right side. We have found that with this technic the tube often passes into the duodenum within 15 to 20 minutes. Occasionally a drink of water facilitates its rapid passage. The tube should be well within the third portion of the duodenum. The duodenal and gastric specimens are collected in two separate graduated by means of a simple suction device attached to a water faucet, with a negative pressure of 50 mm. of mercury (Fig. 1). The patient at this stage may be seated in an arm-chair and the remainder of the test is performed in the sitting position. The tube is provided with many apertures in both the stomach and duodenal portions, which by means of the suction

facilitates the rapid and complete withdrawal of the secretions.

When the tube reaches the duodenum there is ordinarily a fairly active flow of duodenal juice. This activity continues as long as the hydrochloric acid from the stomach enters the duodenum and stimulates the normal secretory activity of the pancreas. The resting state of the pancreatic secretion may be reached only when the gastric juice is withdrawn from the stomach and not permitted to enter into the duodenum. The duodenal flow then becomes very scanty and may drop to zero or to a very minimal quantity, about one cubic centimeter per minute. It is advisable to establish the basal rate of flow for a period of twenty minutes, which usually consists of about twenty cubic centimeters or less.

The secretin is now injected intravenously. The amount of secretin used is a submaximal dose corresponding to one clinical unit ($\frac{1}{2}$ mg.) per kilogram of body weight. The amount required is dissolved in about eight cubic centimeters of sterile normal saline and is brought to a boil several times in five minutes.

I. VOLUME

Immediately following the injection both collecting tubes containing the basal secretion for stomach and duodenum are quickly changed. Within a minute or two the duodenal flow rapidly increases and may rise from five to ten times the basal flow during the first twenty minutes (Fig. 2). If the secretion is bile-stained at the beginning this rapidly disappears

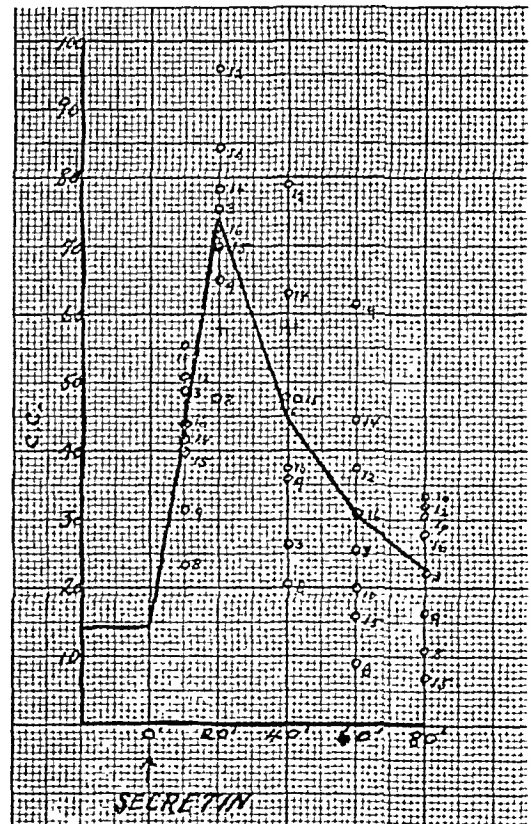
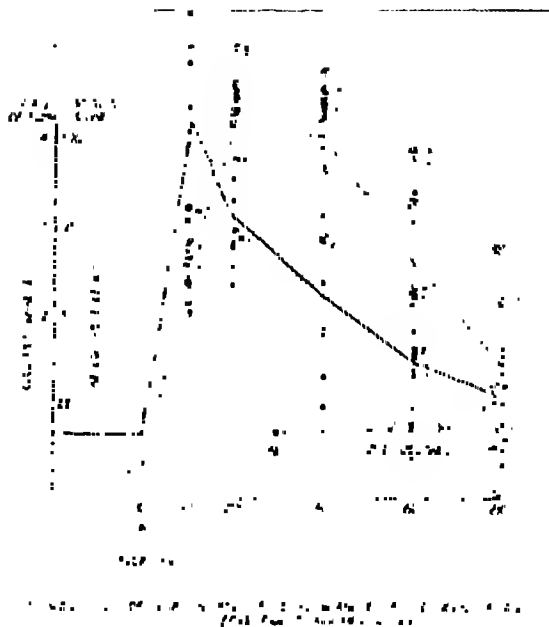


Fig. 2. Effect of secretin on volume of flow.

*Daval Rubber Company.



within the first ten minutes and the erstwhile golden-yellow secretion becomes a clear or slightly opalescent colorless fluid.

After the first ten minutes the tubes are again changed and a second ten minute period is run. The maximum flow is reached within the first twenty minutes after which the volume slowly declines and continues from eighty minutes to two hours before again returning to the basal rate. Towards the end of the eighty minute test period, the bile coloring may reappear.

After the first two ten-minute periods the tubes are changed every twenty minutes for a total period of eighty minutes following the injection of secretin. All tubes are marked and the secretions quantitatively collected. The gastric secretions are saved for the purpose of ascertaining whether there has been any regurgitation of the duodenal juices into the stomach. This is noted by a lowering of the acidity or a change to an alkaline reaction and by bile discoloration.

The total volume of duodenal juice collected is directly proportional to the body weight of the individual. It varied for the eighty minute period in our normal series from 88 to 244 cc. which represents 2.5 to 3.8 cc. per kilogram of body weight.

II. CONCENTRATION OF BICARBONATE

normal series from 88 to 244 cc. which represents 2.5 to 3.8 cc. per kilogram of body weight.

in the basal state, which varies in our series from 0 to 26 milliequivalents per liter, it rises to a maximum varying from 95 to 126 m. eq. per liter at the end of twenty minutes (Fig. 3). The bicarbonate then gradually drops to an average concentration of 37 m. eq. in the last twenty minutes. The bicarbonate concentration approximates the volume of flow and runs a fairly parallel curve. The maximum rise of the bicarbonate, however, appears somewhat later than the maximum volume and falls more slowly (Fig. 3).

The bicarbonate content is determined by titration. Five cubic centimeters of each specimen are titrated against 0.1 N NaOH, after acidification with 10 cc. of 0.1 N HCl. The result is expressed in milliequivalents per liter. The study of the normal bicarbonate concentration curve in duodenal contents which is so essential for the evaluation of normal pancreatic function is only made possible through the use of the double tube which prevents the lowering of the bicarbonate content by the admixture of hydrochloric acid to the duodenal contents.

III. CONCENTRATION AND QUANTITY OF ENZYMES

The effect of secretin upon the pancreatic enzyme secretion is to cause a marked increase in the total output of diastase, trypsin and lipase. During the first ten minute period they rise about eight to nine times (Fig. 4) as compared to the basal or resting secretion. This increase continues throughout the eighty minute period gradually lessening so that in the last twenty minute period it is still about twice that of the basal twenty minute period.

The concentration of the enzymes, however, is inversely proportional to the volume of flow. While the total output rises with the increase in volume the concentration of the enzymes drops. Only in a limited

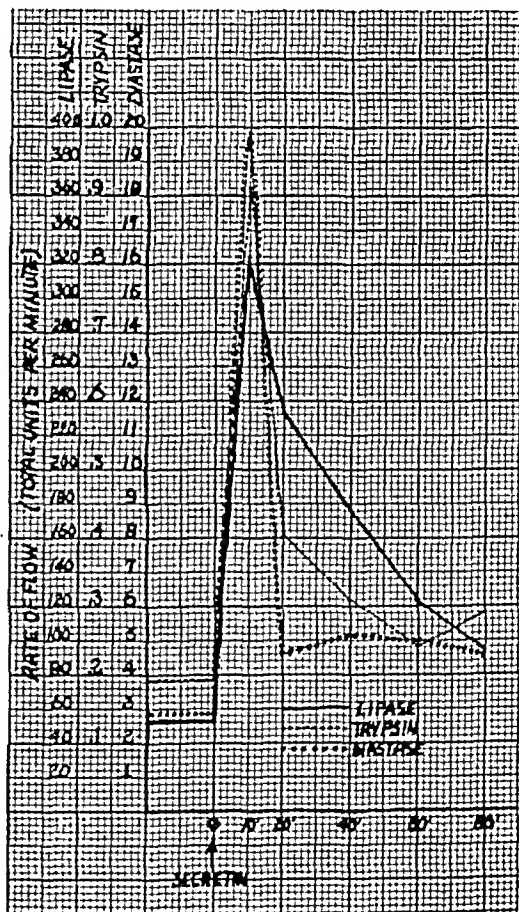
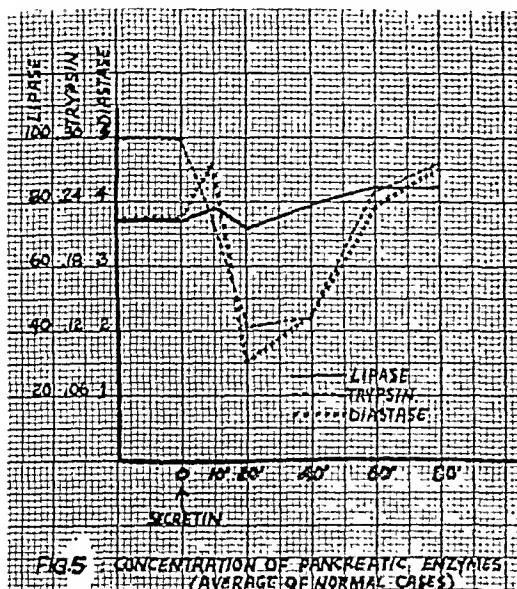


Fig. 4. Effect of secretin upon rate of flow of pancreatic enzymes.



number of cases does the concentration rise slightly in the first ten minute period and this is believed to be due to a washing out of preformed and prestored enzymes in the cells and in the ducts during the resting period. The concentration falls lowest at the end of the first twenty minute period when the volume of flow is high and gradually rises again as the volume of flow diminishes (Fig. 5). The specific action of secretin stimulus upon the enzyme secretion of the pancreatic cell can be gathered from the rise in concentration of enzyme in the last twenty minute period when the volume has already dropped to one-fourth of the first twenty minute period. The behavior of the concentration curves for the three enzymes is uniform with the exception that the lipase curve is flatter, the concentration not dropping to quite as low a level as for the other two enzymes.

In our series of normal cases we found the total amount of enzymes secreted during the eighty minute period expressed in kilograms of body weight to be as follows:

	Lowest	Highest
Diastase	6.1	13.4 units per kg.
Trypsin	.4	.8 units per kg.
Lipase	152.0	231.0 units per kg.

We have accepted these values as the normal standards. The minimal values given have been regarded as the lowest limits for normal cases. However, the maximal values given may go even higher. These findings correspond in the main with the values given by the Swedish investigators. The lower normal limits were identical. The maximal normal limits in their series were higher. These normal values have been derived from the limited material of fourteen cases in this preliminary report. Those of the Swedish group were based upon only fifteen cases. We realize the need of far greater material for further substantiation of these values. We hope to continue these investigations as well as stimulate other workers in this field.

In our investigation we have also included quantitative determination of lipase which has been omitted by the Swedish workers. The importance of making determination of all the enzymes will be seen when we come to study the pathological material.

The methods employed for the determination of enzymes were as follows:

For diastase: Norby's method (14) modified for duodenal contents

For trypsin: Willstatters's method (15)

For lipase: The method of Cherry and Crandall (16) modified by Comfort and Osterberg (17) using a 1:10 dilution.

PANCREATIC RESPONSE TO SECRETIN IN PATHOLOGICAL CASES

Our pathological material consists of one case of obstruction of pancreatic duct (Case I); impacted gall stone at the ampulla of Vater closing the pancreatic duct as well (Case II); carcinoma involving pancreas and gall bladder (Case III); carcinoma of the stomach with metastasis in the liver with marked cachexia (Case IV); two cases of steatorrhea of long standing with marked nutritional disturbances (Cases V and VI); two cases of chronic intermittent diarrhea and vague digestive symptoms (Cases VII and VIII).

We have found that the response to secretin in these cases revealed deficiencies affecting either the total volume, the bicarbonate concentration, or the total quantity of enzymes. Only in rare instances of a complete block of the pancreatic duct by stone or tumor were all the functions simultaneously affected. In all other instances of chronic pancreatic disorders the characteristic finding was a dissociation of functions where one or more were diminished while the other remained normal. This dissociation affects the individual enzymes as well. This a very important finding for it tends to alter the view hitherto held of a simultaneous involvement of all the enzymes in pancreatic affections. In the light of these findings we feel that the estimation of only one enzyme cannot be regarded as an index of all the others.

In the small group of pathological material so far studied the dissociation of the enzymes was a constant finding. In four cases of diarrhea and steatorrhea the

FIGURE VI
Dissociation of pancreatic functions in pathological states

	Vol.	Bicarb.	Diastase	Trypsin	Lipase
Case I	Low (0.3)	Low (26)	Low (0.25)	Low (.05)	Low (23.0)
Case II	Normal (5.5)	Low (90)	Low (5.1)	Normal (.8)	Normal (412)
Case III	Normal (2.4)	Normal (118)	Low (5.4)	Low (.31)	Normal (190)
Case IV	Low (.52)	Low (59)	Normal (10.1)	Low (.2)	Low (43)
Case V	Low (2.3)	Normal (117)	Normal (12.3)	Normal (.53)	Low (32.5)
Case VI	Low (2.1)	Normal (105)	Normal (10.1)	Normal (.4)	Low (62.6)
Case VII	Low (2.3)	Low (87)	Normal (8.5)	Normal (.43)	Low (145)
Case VIII	Low (2.1)	Normal (93)	Normal (10.7)	Low (.2)	Low (145)

lipase was diminished. In half the cases the secretin test was repeated two or three times within a period of several weeks. With the exception of one case, the findings were consistent.

The dissociation as it occurred in our pathological cases may be seen in Fig. 6.

The case histories and the results of the secretin test in this series are as follows:

Case 1. R. P., Female. Aged 72. Admitted to Sydenham Hospital, December 13, 1938, with a two year history of frequent attacks of epigastric pain associated with nausea and occasionally vomiting. The patient was a moderate diabetic and responded to dietetic treatment. On October 4, the patient was awakened in the early morning with a very severe attack of epigastric pain with collapse. Blood pressure fell to 80. Heart sounds poor. Was treated on basis of coronary occlusion. On October 31, about four weeks later, developed a severe chill with temperature of 104°, which subsided in twelve hours. On November 21, three weeks before admission, the patient became jaundiced with progressive deepening of color. Stools acholic.

Physical examination revealed an enlarged liver four fingers below the free costal margin; firm and smooth. Gall bladder distended; easily palpable; not tender. X-ray examination of the gall bladder with the dye, made six months ago, visualized the gall bladder and showed no stones.

Blood Chemistry: Urea—10.2; Sugar—116; Cholesterol—310; Esters—151—49%; Van den Bergh—9.2 mg. Urine: 4 plus bile; trace of urobilinogen.

Glucose tolerance test revealed a high sugar curve of the diabetic type: 303 after 1 hour; 221 after 3 hours.

Secretin test was performed December 21, 1938. There was no response whatsoever to the secretin stimulus. The scanty flow continued in the basal period so that in the eighty minute period only 17 cc. of bile stained juice were collected. The enzyme output was negligible. Shortly after the injection the patient complained of a cramp-like pain in the upper abdomen which lasted about ten minutes. This pain recurred an hour later.

The results were as follows:

Volume	0.3 cc. /Kg./80'
Bicarbonate	26 m.eq. pooled
Diastase	0.25 u/Kg./80'
Trypsin	.05 u/Kg./80'
Lipase	23.0 u/Kg./80'

At the end of the secretin test 35 cc. saturated solution of magnesium sulphate were instilled into the duodenum following which 40 cc. of thick, dark gall bladder bile were collected. After this, the previously palpable gall bladder could no longer be felt.

The patient gradually improved; the jaundice slowly disappeared with the Van den Bergh coming down to 1.9 mg. on December 30, 1938. Patient discharged feeling quite well, January 7, 1939.

The absence of response to secretin, the cramp-like pain during the test and the absence of gall stones led us to believe that there was a complete block of the pancreatic duct associated with a partial block of the choledochus.

Case 2. G. W., Female. Aged 40. History of several attacks of biliary colic. Cholecystogram revealed the presence of calculi. The patient was admitted to Sydenham Hospital, May 5, 1938, with jaundice following a brief attack of colic one week before. Laboratory reports revealed a Van den Bergh of 12 mgs. which in two weeks rose to 16.4 mg. The urine was deeply bile stained, the urobilinogen being persistently absent. The stools were clay-colored. The cholesterol was 215; the esters 103. A duodenal drainage revealed a total absence of pancreatic enzymes indicating a complete blockage at the ampulla of Vater, probably by a calculus. The blood lipase was ele-

vated to 1.5 units. A laparotomy revealed an impacted stone in the ampulla, necessitating the opening of the duodenum for its removal. The patient made a good recovery. Three months later, following a recurrent attack of jaundice lasting several days, the patient again came under observation at which time a secretin test was applied. The findings were as follows:

Volume	5.5 cc. /Kg./80'
Bicarbonate	90 m.eq.
Diastase	5.1 u/Kg./80'
Trypsin	.8 u/Kg./80'
Lipase	412 u/Kg./80'

These results, revealing a diminished diastase and bicarbonate, indicate the persistent pancreatic damage due to the obstructing stone. The blood lipase at this time was more elevated than before, 2.5 units.

Case 3. C. T., Female. Aged 50. Admitted to Sydenham Hospital, October 21, 1938. Three months prior to admission the patient developed painless jaundice with progressive weakness and loss of weight. The stools were clay-colored. The urine contained considerable bile but no urobilinogen. The blood bilirubin was 8.8 mgs. The cholesterol was 158; esters 66. A laparotomy revealed a carcinomatous mass involving the head of the pancreas and gall bladder. A permanent choledocotomy was made to relieve the jaundice.

The secretin test showed a low trypsin, low diastase and a slightly diminished volume.

Volume	2.4 cc. /Kg./80'
Bicarbonate	118.0 m.eq.
Diastase	5.4 u/Kg./80'
Trypsin	.31 u/Kg./80'
Lipase	190.0 u/Kg./80'

Case 4. G. T., Colored male. Aged 49. Admitted to Sydenham Hospital, September 26, 1938. He had received antilietic therapy for five years. History of alcoholism. Onset three months prior to admission with abdominal distension, weakness, loss of weight and intense pruritus. Jaundice, clay-colored stools and highly pigmented urine. Examination revealed a large, hard liver, nodular to palpation, extending to the level of the umbilicus. Masses were also palpated in the left upper quadrant. There was pitting edema of the ankles. The hemoglobin was 58%, red blood cells 3,500,000. The Van den Bergh showed 7.5 mgs. Bile and urobilinogen were both present in the urine. The patient was markedly cachectic. A biopsy of the liver, removed through peritoneoscopy revealed an adenocarcinoma. X-ray of the stomach showed the presence of a large irregular tumor in the antral region.

The secretin test revealed all functions diminished except diastase.

Volume	.92 cc. /Kg./80'
Bicarbonate	59.0 m.eq.
Diastase	10.1 u/Kg./80'
Trypsin	.2 u/Kg./80'
Lipase	43.0 u/Kg./80'

The patient died November 14, 1938. An autopsy revealed a carcinoma of the stomach and liver. The pancreas was small revealing no obstruction in the ducts. A microscopic examination revealed disseminated areas of focal necrosis as well as areas of extreme congestion in the ducts and parenchyma.

Case 5. C. W., Dentist. Single, male. Aged 35. Came under observation November 30, 1938.

The patient first developed frequent bowel movements during the summers of 1931 and 1932, lasting several weeks and requiring medical attention. In August, 1933, shortly after returning from a trip to Florida, the patient took ill with vomiting, diarrhea and general abdominal discomfort. The illness was progressive with loss of weight and strength. Several months later the patient underwent an exploratory laparotomy for suspected carci-

noma of the stomach. Nothing was found. The patient was hospitalized for three months during which he required a blood transfusion. He left the hospital unimproved with persistent diarrhea of five to six bowel movements daily. The stool was light in color, frothy, strongly acid with fetid odor. In May, 1934, May 1935, and December, 1937, the patient was admitted to different hospitals because of exacerbation of the symptoms. In 1934 the diagnosis of non-tropical sprue was made and the patient was put on a banana and strawberry diet. In 1937 this diet was repeated and associated with intensive liver therapy. During this period of hospitalization the patient again received two blood transfusions because of debility and anemia.

During the past year the symptoms continued with three to five bowel movements daily. Stools were bulky, light gray in color and contained large quantities of neutral fats and microscopically large numbers of meat fibres. No blood, pus or parasites or ova were found. Blood examination showed no eosinophilia. Gastric analysis revealed an absence of free hydrochloric acid. Proctoscopy and sigmoidoscopy were persistently negative. X-ray examination of the gastro-intestinal tract was negative.

A secretin test performed on November 30, 1938, revealed a deficiency in lipase. The volume was only slightly diminished. Otherwise all the functions were normal.

Volume	2.3 per Kg./80'
Bicarbonate	117 m. eq.
Diastase	12.3 u Kg. 80'
Trypsin	.53 u Kg./80'
Lipase	32.8 u Kg./80'

Another interesting finding in conjunction with the secretin test was the presence of motile *Giardia intestinalis* in the duodenal contents upon microscopic examination. This is in all probability a secondary infestation.

Case 6. T. DeR., Housewife. Aged 38. For the past two years the patient complained of "nervous feeling in the stomach" accompanied by loose bowels. The bowel movements increased in frequency, four to five and occasionally ten per day. The stools were liquid, foul smelling, light yellow in color. No blood or pus were noticed. She had lost twenty pounds. The gastric analysis revealed no free hydrochloric acid, total—12. Proctoscopy and sigmoidoscopy showed slight congestion. There was no evidence of ulcers. The X-ray examination of the gastro-intestinal tract was negative. The stool contained large quantities of neutral fats and microscopic examination revealed large numbers of meat fibres. The duodenal contents, during the secretin studies, revealed the presence of monilia albicans.

The secretin test performed December 12, 1938, revealed a marked lipase deficiency. The volume was slightly diminished.

Volume	2.1 cc. per Kg./80'
Bicarbonate	105 m. eq.
Diastase	10.13 u Kg. 80'
Trypsin	.40 u Kg. 80'
Lipase	69.6 u Kg. 80'

Case 7. S. F., Female. Aged 35. Single. School teacher. The patient began complaining twelve years ago of morning nausea and vomiting. She also developed attacks of diarrhea every summer. More recently she complained of diarrhea associated with abdominal colic. She experienced digestive discomfort with pain in left upper quadrant, referred to the back. There was loss of weight and strength. The present weight was 101 pounds. Anorexia. Examination revealed:

Gastric acidity: free HCl—28; total—46
Proctoscopy: negative

X-ray series of the gastro-intestinal tract and gall bladder: negative

Stools: light in color, fetid, containing large amounts of neutral fats.

Secretin test on August 24, 1938, revealed a low bicarbonate, low volume and slightly diminished lipase.

Volume	2.26 cc. /Kg. '80'
Maximum bicarbonate	87 m.eq.
Diastase	8.5 u/Kg./80'
Trypsin	.43 u/Kg./80'
Lipase	148.0 u/Kg./80'

Case 8. S. Z., Housewife. Aged 44. The patient began complaining several years ago of gaseous eructation and abdominal distress; frequent attacks of loose bowels associated with pain in the left hypochondrium and lower preordium and back, at times very distressing. Examination revealed a gas-distended cardia with elevation of the left diaphragm after a gastro-intestinal series.

Stools contained increased fats. The gastric analysis showed a free acidity of 30; total acidity of 40.

A secretin test on September 30, 1938, revealed a low volume, markedly low trypsin and slightly diminished lipase.

Volume	2.1 cc. /Kg. '80'
Maximum bicarbonate	93 m.eq.
Diastase	10.7 u/Kg. 80'
Trypsin	.2 u/Kg. 80'
Lipase	148.0 u/Kg. '80'

DISCUSSION

In secretin we possess a valuable method for determining the state of pancreatic activity. When secretin is injected intravenously in the normal individual there follows a prompt physiological response characterized by increased volume of flow, high concentration of bicarbonate, and increased total enzyme secretion. The reaction of the pancreas to secretin is as specific as is that of the gastric cell to histamine. The increased output with slight variations is proportional to the body weight of the individual and standards are established which may be considered as normal values.

In the abnormal states we find this test to be of inestimable value in the detection of cases of chronic pancreatic disorders which have hitherto escaped recognition. Many diarrheas frequently attributed to emotional and gastrogenic causes, to non-tropical sprue, idiopathic steatorrhea may now be shown in light of this work to be of pancreatic origin. The inability in the past of obtaining pure uncontaminated pancreatic juice, the lack of study of the bicarbonate concentration and of the total enzyme output as well as the lack of standardization per given time and body weight have retarded our knowledge and made the study of pancreas vague and incomplete.

With the gastro-duodenal tube method we are able to remove the acid gastric secretions which would otherwise markedly lower the pH values in the duodenum and cause interference with the optimum enzyme activity. The suction method and the specially constructed tube enable us to remove the total quantity of pancreatic and duodenal juices which are so essential to the quantitative studies and standardization of the secretion.

We also find the test to be of great value in recognizing mechanical obstruction of the pancreatic duct

when occluded either primarily or simultaneously with common duct obstruction such as occurs in impaction of stones in the ampulla of Vater or pancreatic tumors involving both ducts. The simultaneous absence of bile and pancreatic juices point to a surgical type of obstruction and indicate immediate exploration. The delay in the relief of such pancreatic duct obstructions may lead either to acute pancreatic involvement or possible residual chronic pancreatic disturbance, as is noted in Cases 1 and 2.

The application of the test is of further aid in differentiating the normal from a non-functioning gall bladder. Through the choleretic effect of secretin and the absence of a cholecystokinetic factor, the increased flow of bile enters and is stored in the normally functioning gall bladder. In cases of non-functioning gall bladder the bile admixes freely with the pancreatic secretion.

The field for the study of chronic pancreatic disturbance becomes unlimited when we also consider the large group of cholecystectomized individuals who persist with symptoms of pain and distress, in whom the surgeon has previously reported a hardening of the pancreas, and in whom ordinary methods of examination have given little clue so far as to the nature of the recurring symptoms.

Our studies tend to indicate that the practice heretofore followed of estimating only one enzyme as an index of the total pancreatic capacity was inadequate. We find a dissociation in all the functions of the pancreas. One or more of the enzymes, or any of the other functions may be independently affected. One may state that under pathological conditions there exists an instability in the response of the pancreatic cell with regard to enzyme output characterized by dissociation of the enzymes affecting particularly lipase and trypsin and least the diastase. There is also a variability in the output of the deficient enzymes so that one may be affected more than the other during repeated examination.

In the limited number of steatorrhea cases the lipase was found to be diminished. The material, however, is too limited for general deductions at the present time and a far larger number of cases will be

required, with frequent repetitions of the test, before making final conclusions.

The injection of secretin appears also to be of therapeutic value. We have noted in several instances a marked clinical improvement after its use. In several cholecystectomized patients with persistent symptoms the injection was followed by a period of complete relief of all digestive symptoms lasting as long as six weeks.

The test can be readily carried out as an office procedure. By pooling aliquot portions of the samples one determination may be made for each of the enzymes for the entire period. The procedure is then considerably simplified. With further studies there is a possibility that the time factor may also be shortened.

SUMMARY AND CONCLUSIONS

1. Studies of pancreatic function in normal and abnormal cases have been carried out by means of secretin test.

2. A specially devised double gastro-duodenal tube has been employed in the collection of the pancreatic secretion. This tube prevents interference which might otherwise occur from the admixture of the acid gastric juice.

3. An intravenous injection of secretin ($\frac{1}{2}$ mg. per kg.) is immediately followed by an increased volume of secretion, a high concentration of bicarbonate, and an increased output of all the enzymes.

4. The response of the secretions is proportionate to the body weight of the individual and the values given may be regarded as the normal standards.

5. In the pathological state one or more of the functions may be impaired. This dissociation affects the enzymes as well. There is no uniformity in their behavior and therefore all enzymes must be simultaneously studied for the detection of any aberration in pancreatic function.

Note: We are indebted to Miss Clare Lowenberg, M.Sc., for her valuable and painstaking work in executing the enzyme determinations and for her indispensable aid in the chemical studies of this work. We also wish to thank Dr. Irving Madoff for his valuable assistance with the many chemical estimations.

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The Surgical Treatment of Biliary Tract Disease*

(a) Acute Cholecystitis

By

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THE indications for surgical treatment of biliary tract lesions are not satisfactorily standardized. This is evident from the debates still current on cholecystostomy versus cholecystectomy, cholecystectomy with or without drainage, the advisability of routine exploration of the ducts in biliary tract operations, the indications for and duration of drainage of the common duct, the indications for operation on the acutely inflamed gall bladder, etc. The factors which will probably be of greatest importance in developing criteria of procedure will arise from the critical survey and analysis of methods and end results in large series of personally observed cases.

Within recent years the treatment of acute cholecystitis has become the subject of considerable controversy because evidence which contradicts older con-

inflammation, the criteria of which were congestion, oedema and margination and emigration of leucocytes, through all gradations of congestion, oedema and thickening of the wall of the organ, with or without a peritoneal reaction (fluid and exudate) necrosis of the mucosa, leucocytic infiltration, and even abscesses in the wall. Similarly, a gangrenous gall bladder was one in which there was not merely a greenish exudate on the serous surface of the wall, but actual death of the tissue wall, grossly and microscopically.

Of these 1500 cases there were 341 cases of acute cholecystitis in all of which cholecystectomy was performed. The large majority of the cholecystectomies were done from below upward. In a comparatively few so much distortion was found that it was deemed

TABLE I

Clinical-Pathological Classification	No. Males	No. Females	Total No.	No. Male Deaths	No. Female Deaths	Total No. Deaths	Perc. Mortality	
Acute cholecystitis	4	4	8	1	1	2	25.00	Acute 341 cases
Acute cholecystitis with cholelithiasis	26	283	309	4	23	27	8.74	Total deaths 32
Acute cholecystitis with cholelithiasis and choledocholithiasis	3	21	24	1	2	3	12.50	Mortality 9.3%

cepts is continually being adduced. No longer can it be claimed that most cases of acute cholecystitis would subside if treated conservatively, or that gangrene and perforation are rare complications. Already compilations of carefully studied cases in increasingly large numbers yield figures which indicate a necessity for revising those views. Further similar study will eventually yield enough data, analysis of which will enable standardization of procedure.

We have just completed a study of 1500 cases of disease of the gall bladder and biliary ducts operated on between July 1, 1928, and December 31, 1937, a period of nine and a half years. Not only were all of these cases observed and operated on by us, but their records were personally dictated, thus insuring a uniformity of terminology. In all of them, the final diagnosis under which the case was classified was an anatomical diagnosis. Thus, to be included under the heading of acute cholecystitis, a case must have had characteristic pathological gross and histologic findings. These varied from the mildest forms of acute

safer to dissect the gall bladder free from its bed first so as to aid in identification of the hepatic and common ducts. In all, however, as an integral part of the procedure, the common duct was explored. Palpation alone was demonstrated to be woefully inefficient, particularly in the presence of induration about the duct. In every case a probe was passed through the duct and palpation against the rigid, resistant metal often revealed stones which would otherwise have escaped recognition. Of the 341 cases in the acute group 21 instances, or 6% of common duct stones were recognized and removed by choledochostomy (Table I).

We are firmly convinced that there are no dangers in probing the ducts. It has been suggested that in acute cholecystitis probing may carry the infected material down into the ducts and produce cholangitis not already existent. To us it would seem strange if the infected material had not already found its way into the duct system in all cases excepting those frankly stenosed at the cystic duct by either inflammation or stone. We feel strongly that any cholecystectomy which is not accompanied by the most "fool-proof"

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TABLE II
Acute cholecystitis

Classification	No. Male	No. Female	Total No. Cases	No. Male Deaths	No. Female Deaths	Total No. Deaths	Mortality Per Cent
Acute cholecystitis	14	142	156	1	4	5	3.20
Acute empyema	1	40	41	0	2	2	4.87
Acute gangrenous cholecystitis	11	97	111	3	13	16	14.41
Acute perforation	4	29	33	2	7	9	27.27
Total	33	308	341	6	26	32	9.38

attempt to ascertain the existence of stones in the ducts is definitely an incomplete procedure.

The total mortality in the 341 cases was 9.4%. An analysis of the components contributing to this high mortality reveals some interesting facts. 156 of these cases were acutely inflamed, but did not have any gangrene or were not perforated, and in this group the mortality was 3.2%. In the acute gangrenous cholecystitis present in 111 instances, however, there was a mortality of 14.4%, and in the cases of acute perforations encountered in 33 instances there was a mortality of 27.27% (Table II).

In only one instance of the 111 cases of gangrenous cholecystitis did we find complete gangrene of the entire gall bladder. In the others the gangrene was patchy. This seems to indicate that the usual gangrenous change of local patchy ischemia is not the result of embolization or thrombosis of the main trunk of the cystic artery, but rather the end product of local inflammatory activity. Or, worded differently, the gangrenous lesion is not present from the onset of the disease but comes later, after inflammation has existed for some time, long enough for the development of local factors (oedema, etc.) which then deprive isolated patches of tissue of blood supply.

Since, therefore, both the gangrenous lesion and the perforation are sequelae to the acute inflammation, it becomes evident from the mortality statistics that the cases operated early in the acute phase, before the onset of these complications, have a much better prognosis (Table III).

This would settle the question of procedure were it not for the fact that not all cases of acute cholecystitis progress to gangrene and perforation. Indeed, many subside completely. It then becomes necessary to seek means of recognizing the impending onset of gangrene and perforation. If one could do so, then despite the great frequency of gangrene as shown in more recent reports, it would be feasible to separate the two groups and treat one expectantly and the other by immediate operation. Such ideal diagnosis and therapy should markedly diminish the total mortality.

As a result of careful study of many cases, it has become possible to generalize regarding the clinical differences by means of which gangrenous or perforated gall bladders may be distinguished from the simple acute variety. In general, the former have higher temperatures, higher white cell counts, are more likely to have palpable gall bladders, and have had a longer course. In the individual case, however,

there is frequently no parallelism between the clinical course (signs and symptoms) and the pathological changes going on in the gall bladder. Thus it is found that gangrene occurs in the presence of moderate symptoms whereas it may be absent in cases presenting severe clinical manifestations of infection. In specific instances, therefore, there may often be no distinctive signs or symptoms which mark the transition from the non-gangrenous to the gangrenous stage of acute cholecystitis. Under such circumstances conservative expectancy becomes dangerous. Such treatment is predicated on the hope that the inflammation may subside. It would seem that the occurrence of gangrene and perforation 144 times in 305 cases of acute cholecystitis should discourage such hope.

Wesson and Montgomery (1) reported on 76 cases of acute cholecystitis operated on at the Mayo Clinic in a two and a half year period. Of this number there were "twenty-two cases in which the diagnosis before operation was chronic cholecystitis but at the time of operation the surgeon's diagnosis was acute cholecystitis." Three of these 22 cases were gangrenous and perforated, yet their clinical signs and symptoms were such that the acute lesion wasn't recognized before operation.

The impression has been created that patients with acute cholecystitis are poor operative risks. For this reason, and also because of alleged technical diffi-

TABLE III
INCIDENCE OF COMPLICATIONS, PERCENT OF THE SURVIVORS

27.27%

14.41%

4.87%

3.20%

Acute Cholecystitis
156 casesAcute
empyema
41 casesAcute gangrenous cholecystitis
111 casesAcute
perforation
33 cases

MORTALITY PERCENTAGES

culties, cholecystectomy has often been delayed, and in those cases where operation was deemed imperative, cholecystostomy was frequently advocated as the lesser evil. Our results indicate that this is not so. A mortality of 3.2% in the 156 cases of cholecystectomy for acute cholecystitis without gangrene or perforation is not particularly high. However, properly to judge the risk of cholecystectomy in this series, 3 cases should

TABLE IV

Reoperation in those patients with previous cholecystostomy

	No. Cases	No. Deaths	Per Cent Mortality
Acute cholecystitis with cholelithiasis	4	3	75.00
Acute gangrenous cholecystitis with cholelithiasis	4	2	50.00
Acute gangrenous cholecystitis with walled off perforation	1	2	50.00
Chronic cholecystitis with cholelithiasis	13	2	15.38
Chronic cholecystitis with cholelithiasis and choledocholithiasis	3	2	66.66
Chronic cholecystitis with carcinoma of gall bladder and cholelithiasis	2	1	50.00
Total	30	12	40.00

be eliminated from consideration. These were cases of acute hemorrhagic pancreatic necrosis with accompanying acute cholecystitis, fully reported elsewhere (2), in which the operation consisted not merely of cholecystectomy but also of choledochostomy with T-tube drainage, mobilization of the duodenum for exploration of Wirsung's duct, splitting the capsule of the pancreas and drainage. They therefore do not represent mortalities from cholecystectomy alone nor do they represent acute cholecystitis alone. They represent a very serious disease, the mortality of which in large series ranges between 22 and 78%. With their elimination from the series, the mortality becomes 2 out of 153 cases, or 1.3%. This figure, comparing favorably with the best figures for cholecystectomy in chronic cholecystitis, refutes the contention that cholecystectomy itself is fraught with more danger in the acute than in the chronic case, and in no way supports the idea that the patient has greater difficulty in accommodating to the operation in the presence of an acute infection. Of cholecystostomy more will be said later. Similarly, in the group of

acute empyema, one case fully described elsewhere (3), represents a death from pyelophlebitis and multiple liver abscess which was already existent at the time of operation, when not only was the gall bladder removed, but also the abscesses were drained. Deducting this death from the series leaves 1 death in 41 cases of cholecystectomy for empyema, or a mortality of 2.5%.

All of these patients had cholecystectomies. If the mortality rate for cholecystectomy in the 156 acute cases is not sufficient to eliminate cholecystostomy from consideration in the surgical treatment of the acute lesion, then one should consider the serious problem of the patient who has had a previous cholecystostomy and subsequently needs reoperation. At the first operation cholecystostomy was performed because it was assumed to offer a better chance for life than would cholecystectomy. Numerous statistical studies were published to demonstrate the greater safety of the former procedure. All of the studies which presented that point of view, however, did not go far enough, in that they failed to consider the frequency of reoperation necessitated by the incompleteness of the primary therapy, and the appalling mortality of the secondary procedure. We have had 30 such cases which are analyzed in Table IV, 12 of whom died, giving a mortality of 40%. Would 12 of those 30 have died at the primary operation if cholecystectomy had been done? Even if it were assumed that at the primary operation all of these patients had the worst type of acute lesion; i.e., the gangrenous and perforated gall bladder (Table V), our figures show that a lower mortality rate than 40% could have been expected from cholecystectomy, and at least the difference between the two rates must be attributed to the previous cholecystostomy. This alone does not indicate that cholecystostomy may not be safer than cholecystectomy in large groups of cases. It would be necessary to determine the frequency with which cholecystostomy is subsequently followed by symptoms and cholecystectomy. Manifestly we have no statistics of our own to go by. Dieterich (4), however, reported 384 cholecystostomies in a 30 year period with 50 deaths, a primary mortality of 13%. (This mortality rate is only slightly worse than that of Darnier & Cullen (5) who reported 10% in 290 cases of cholecystostomy where only 17 gall bladders were found to be gangrenous). In the remaining 334 it was necessary to reoperate in 45 instances or in 13%. An analysis of these 45 cases revealed that stones had been left in 43 of them.

TABLE V
Perforated gall bladders

	No. Male	No. Female	Total No. Cases	No. Male Deaths	No. Female Deaths	Total No. Deaths	Mortality Per Cent
Acute walled off perforation	3	21	24	1	3	4	16.66
Acute freely perforated	1	8	9	1	4	5	55.55
Total	4	29	33	2	7	9	27.27

If we were to consider that the 30 cases reoperated by us represented 13% of cases previously subjected to cholecystostomy without any primary mortality, then the total number of cholecystostomies would have been 230. Since 12 of the 30 died, 12 in relation to 230 would make a delayed mortality of 5% for the whole group. If this be added to Dieterich's primary mortality rate of 13%, it would make a total of 18%, which would certainly not justify cholecystostomy. This type of calculation would give a much higher mortality rate if Catell's (6) figures were used instead of Dieterich's. Catell reports on 60 patients with cholecystostomy, 43 or 72% of which, had a recurrence of symptoms and 21, or 32%, were reoperated.

From the standpoint of mortality alone, our 30 would have fared better with cholecystectomy. The interval between operations, however, must also be considered. These patients were sick during that interval and, while 11 were reoperated during an acute attack, 19 of them were driven to reoperation for relief from their chronic symptoms. In the light of this analysis, cholecystostomy cannot be justified under any circumstances excepting perhaps to decompress the biliary tract in acute pancreatitis in the absence of cholecystitis, cholelithiasis and choledocholithiasis (2).

SUMMARY

Pathologically acute cholecystitis is frequently a progressive lesion proceeding to gangrene and perforation.

The severity of the lesion in the individual case is usually not predictable from the clinical symptoms and signs.

The mortality from cholecystectomy in the presence of the acute lesion without complications is very low and becomes progressively greater when gangrene and perforation occur.

The danger of operating on the patient in the acute stage before gangrene and perforation is considerably less than the danger of development of gangrene and perforation with their attendant high mortality.

Consideration of its primary mortality, subsequent morbidity, high percentage necessity for reoperation and high mortality at subsequent reoperation eliminates cholecystostomy from consideration in the treatment of acute cholecystitis.

Our observations confirm the opinions of those who have advocated early operation in acute cholecystitis, among whom are notably Walton (7), Bland-Sutton (8), Kirschner (9), Crile (10), Miller (11), Alexander (12), Graham (13), Mentzer (14), Zinninger (15), Judd and Phillips (16), Stone and Owings (17), and particularly Heuer (18), whose analysis is probably the best to date.

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The Surgical Treatment of Biliary Tract Disease*

(b) Chronic Lesions

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CHRONIC CHOLECYSTITIS

OF the 1500 cases of diseases of the gall bladder and biliary tract operated by us in the 9½ year period ending December 31, 1937, 1072 were cases of chronic cholecystitis. They were so classified because of the histologic findings rather than clinical appearance. 942 of them were cases not only of chronic cholecystitis, but had as complications cholelithiasis, choledocholithiasis or both. In the entire group there was a mortality of 3%. This was subdivided as shown in Table I, from which it is noticed that the great con-

tributing factor to the mortality were those cases in which operation had to be done for choledocholithiasis.

Procedure

In all of these cases cholecystectomy was performed. If there is no definite reason for believing that there are stones in the common duct and if in the gross manipulation of preparing the field for cholecystectomy no stones are palpated in the common duct, our procedure consists of drawing the gall bladder up into the wound by ring-clamps placed on the fundus and the ampulla. This exposes the cystic duct which is clamped slightly above its junction with the common

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duct. The cystic duct is then cut half-way across between the clamp and the common duct and a bent probe passed through the opening into the common duct and down to the duodenum, against which the finger palpates for stones. Some bile wells up from the duct occasionally, and this is caught on a stick-sponge. If the clamp is not placed distally on the cystic duct before it is cut, bile and calculi will escape into the peritoneal cavity from the gall bladder. If, after palpation against the probe, calculi are found in the common duct, the latter is opened, either directly or through the stump of the cystic and the stones are removed. Then the duct is drained or closed, depending upon factors to be discussed later, and the cholecystectomy is completed by ligating the vessels and excising the organ.

If, however, stones are easily recognized in the common duct, before the cystic duct has been opened, the gall bladder should be drawn forward as above by both ring-clamps and the cystic duct isolated and clamped. Now instead of cutting across the cystic, the common duct is opened directly, the stones removed, the T-tube inserted and the duct sutured snugly around it, and then the cholecystectomy is performed. Here the preliminary clamping of the cystic duct prevents stones from passing into the common duct from the gall bladder in the interim between the time the T-tube is inserted and the cholecystectomy begun.

Mortality

Of the total number of 1072 cases of chronic cholecystitis, there were 33 deaths, giving an uncorrected mortality of 3%. Of this number, however, 93 cases had choledocholithiasis with common duct drainage, and 18 had previous cholecystostomies. If these two groups of cases totalling 111 were deducted from the 1072 cases, there would be left 961 cases in which there was a total number of 21 deaths, or a mortality of 2%.

It was pointed out in a previous paper (1) that whereas the operation of cholecystectomy for acute cholecystitis itself carries with it a certain inherent small mortality rate, that rate rises when the cases

cease to be ones of simple acute cholecystitis but become complicated. This is also true for chronic cholecystitis. For example, in the 93 cases of chronic cholecystitis with choledocholithiasis, there were 7 deaths, or 7.5% (Table I) and in the 18 cases of chronic cholecystitis which had previously been subjected to cholecystostomy (in two of which there was not only cholelithiasis but also carcinoma of the gall bladder) there were 5 deaths, or 28% (1).

A history of repeated attacks of colic and a long drawn out story of epigastric distress, heartburn, belching, etc., is typical of chronic cholecystitis. Rare indeed, is it that common duct stones or even carcinoma are found in the absence of a previous history referable to biliary tract disease. Since the complications develop after the original disease has been established, it again becomes apparent that the sooner cases of chronic cholecystitis are subjected to cholecystectomy, the lower the mortality from the operative procedure will be.

Early cholecystectomy in chronic cholecystitis would eliminate common duct stones (excepting the metabolic type) as complications, and carcinoma of the gall bladder obviously could not develop in the organ's absence. This does not mean the advocacy of prophylactic cholecystectomy in the absence of lesions, but it does indicate a serious objection to the medical treatment of cholelithiasis. Delay of operation allows for the development of complications, the operative treatment of which raises the mortality.

COMMON DUCT OBSTRUCTION FOLLOWING PREVIOUS CHOLECYSTECTOMY

There were 55 cases of common duct obstruction due either to calculi or to previous operative stenosis. All of them showed varying degrees of jaundice. All of them had had previous cholecystectomy some time from 2 months to 9 years before admission for re-operation (Table II).

Stones

In the 34 cases in which the obstruction was due to stones, there was a marked increase in the transverse diameter of the common duct. In all of them the

TABLE I

Clinical-Pathological Classification	No. Males	No. Females	Total No.	No. Male Deaths	No. Female Deaths	Total No. Deaths	Per Cent Mortality	
Chronic cholecystitis	9	121	130	0	3	3	2.30	Chronic 1072 cases
Chronic cholecystitis with cholelithiasis	112	757	849	3	20	23	2.70	Total deaths 33
Chronic cholecystitis with cholelithiasis and choledocholithiasis	7	86	93	1	6	7	7.46	Mortality 3.07%
Common duct obstruction per se	9	58	67	4	5	9	13.11	Common duct obstruction 67 cases 9 deaths
Carcinoma of gall bladder	3	17	20	1	8	9	45.00	Carcinoma of gall bladder 20 cases 9 deaths

common duct was opened, the stones removed and T-tube drainage instituted. It is exceedingly important, of course, to remove all the stones in the biliary duct. Not infrequently, when one stone is well lodged in the ampulla, the ducts dilate to surprisingly large diameters, and other stones may float back into the hepatic duct. In most instances stones lodged in the ampulla can easily be pushed back into the common duct by gentle manipulation. Occasionally, however, a stone will resist all such attempts. Under such circumstances it can easily be removed by trans-duodenal approach. The duodenum is opened at a point just above the ampulla, the ampulla is slit, the stone removed and the duodenum closed. This was done in four cases in our series. There was one unusual case of intrahepatic lithiasis described elsewhere (2) which, besides common duct calculi, had intrahepatic stones, one of which was 7 cm. long and 2 cm. in diameter. Such stones despite their size may easily go undiscovered. Additional safeguards against overlooking stones in dilated ducts (beside the usual probing) consist of palpation with the index and middle fingers in the foramen of Winslow while a curved clamp is passed through the common duct and through the sphincter of Oddi into the duodenum, and the passage of a catheter to which suction is applied, into the common duct and up into the hepatic ducts. Not infrequently the latter maneuver has drawn a stone down from the hepatic ducts which previously could not be palpated because of its intrahepatic position.

When the patients are returned from the operating room, the long arm of the T-tube is connected by rubber tubing to a bottle at the side of the bed for subaqueous drainage. How long the T-tube shall be left in situ depends upon the conditions found at operation. If the extra-hepatic biliary passages are not very widely dilated at the time of operation, the T-tube is left in place until the bile coming through is clear and until the temperature has dropped to normal. It is then clamped off for a day or two, after which, in the absence of any adverse symptoms, it is withdrawn. If the bile ducts are found to be markedly dilated at operation, it is advisable to keep up T-tube drainage

for a longer period of time. In such patients, as soon as the temperature drops to normal, it is advisable to fill the biliary passages with thorotrast, or other opaque medium, and obtain a roentgenogram for subsequent comparisons. By repetition of this procedure later, it can easily be seen that one of the important results of prolonged drainage, particularly if the patient happens to have a high sphincter of Oddi resistance, is a marked diminution in the transverse diameter of the extra and intrahepatic biliary passages. Our method for determining the resistance of the sphincter of Oddi has already been described (3). As a result of such comparisons it is seen that in the average case, drainage for about 12 or 14 days produces a pronounced diminution in the caliber of the biliary passages at which time, unless the case presents unusual features, the T-tube may be removed. Deaver (4) once kept a T-tube in a common duct for 7 years. In one of our cases described elsewhere (3), drainage was maintained through a T-tube for 16 months. This case was one in which two previous operations had been performed on the gall bladder and common bile duct and in which, at the third operation, the common duct was found to be dilated to a diameter of $1\frac{1}{2}$ cm. and filled with calculi, as were also the hepatic ducts. The unusually slow return to a smaller diameter, as shown by repeated roentgenograms with thorotrast, was responsible for the prolonged drainage.

Stenosis

There were 11 cases of common duct obstruction with jaundice due to stricture following injury to the duct at the original operation. In all of them the stricture was excised. Then one short arm of a T-tube was passed into the proximal portion of the duct, the other into the distal portion and the long arm was conducted out of the abdomen. The ends of the duct were united by suture circumferentially over the tube, excepting where it was necessary to allow for exit of the long arm. The anastomosis was reinforced by a piece of omentum. The T-tube was left in situ for 6 weeks before removal. In all, the results were satisfactory.

Of the 34 cases of obstruction due to stones, there were three deaths, or 8.8% mortality, and in the 21

TABLE II
Common duct obstruction per se

Common Duct Obstruction	No. Male	No. Female	Total No. Cases	No. Male Deaths	No. Female Deaths	Total No. Deaths	Mort. Per Cent	
Calculi	0	34	34	0	3	3	8.82	55 Cases 4 Deaths
Operative Stenosis	1	20	21	0	1	1	4.76	7.27% Mortality
Carcinoma of Duct	1	0	1	1	0	1	100.	12 Cases 5 Deaths
Carcinoma of head of Pancreas	7	4	11	3	1	4	36.36	41.66% Mortality
Total	9	58	67	4	5	9	13.43	

Except for the carcinomas in this chart, all the others had previous cholecystectomies varying from 2 months to 9 years before admission to hospital. Common Duct Obstruction—not due to carcinoma only 7.27% mortality.

cases of operative stenosis there was 1 death, or 4.8% mortality.

CHOLANGITIS FOLLOWING PREVIOUS CHOLECYSTECTOMY

There were 10 other cases which, also having had cholecystectomies previously, were admitted suffering from jaundice, pain in the upper right quadrant and acholic stools and septic temperature. In these cases the common duct was found to be widely dilated, containing no stones, but containing pus and bile. All of these cases of cholangitis were treated by T-tube drainage of the common duct. The symptoms rapidly subsided but the drainage tube was not removed until there was clinical recovery, clear bile flowed freely and three successive days without recurrence of symptoms elapsed after the external arm of the T-tube was clamped off. There were no fatalities.

COMMON DUCT OBSTRUCTION BY CARCINOMA

There were 12 cases of common duct obstruction due to carcinoma. Carcinoma of the duct was found in one instance and carcinoma of the head of the pancreas in 11 instances. All of these cases showed a progressive painless jaundice but, in 20% of the cases of common duct obstruction due to calculi, there was also a painless jaundice, so that it might be mentioned in passing that Courvoisier's Law cannot always be depended upon to make the differential diagnosis between carcinoma and stones in common duct obstruction.

In the obstruction due to carcinoma of the duct, excision of the carcinoma with reimplantation of the proximal portion of the duct into the duodenum was accomplished, but the patient did not survive.

Carcinoma of the head of the pancreas metastasizes very slowly and grows relatively slowly. In a very large percentage of these cases, the patient suffers very severely from the itching of the jaundice. Many of them can be given relief for a long period of time by cholecystenterostomy and should not be denied such relief. Under favorable circumstances the carcinomatous head of the pancreas, with a portion of the duodenum surrounding it, can be resected successfully by a ligation of the common duct, the establishment of a cholecystenterostomy and a gastrojejunostomy. Although a very formidable procedure, its applicability will probably increase. In the 11 cases of carcinoma of the head of the pancreas, there were three mortalities from cholemia despite a cholecystenterostomy, and one mortality following an attempt at radical operative removal of the head of the pancreas.

CARCINOMA OF THE GALL BLADDER

There were 20 cases of carcinoma of the gall bladder and 19 of them had long standing cholelithiasis. Four simply had biopsies done while 16 were subjected to cholecystectomy. In one of the 16, the common duct was opened and drained after stones were removed. In 4 instances the neoplasm had invaded the liver by direct extension, and here a portion of the liver extending at least 2 cms. beyond the recognizable margins of the tumor, was removed with the latter and the gall bladder in one mass. In this group there were 9 deaths, or a mortality of 45.00%, amongst which were two of the cases of partial hepatectomy.

ANESTHESIA

All of the 1500 cases were operated under spinal anesthesia. If, where multiple operations are neces-

sary, they can be performed before sensation is recovered, obviously the criticism of additional anesthesia for the complementary procedure cannot be held up as an objection. Thus in one of these cases (No. 32020) it was possible to do a cholecystectomy for stones, a Polya subtotal gastrectomy for "kissing" ulcer of the pylorus, an appendectomy, and a hysterectomy and bilateral salpingo-oophorectomy for fibroids and chronic pelvic inflammatory disease, all after one spinal injection of neocain. Indeed, the criticism should be in the other direction that so often much of the spinal anesthesia is wasted because it endures so much longer than is necessary for the average procedure.

That this anesthetic is safe and is ideal for biliary tract surgery has long been our belief on the basis of considerable clinical and experimental experience (5, 6, 7, 8, 9, 10, 11). No other anesthetic gives as good relaxation and exposure, and both of these qualities greatly simplify any technical procedure. Since good relaxation and exposure also minimize handling and therefore trauma to tissues, and make smoother the post-operative course, no other anesthetic gives as easy a post-operative convalescence.

DRAINAGE

The problem of drainage following cholecystectomy is one that deserves discussion. Up to 12 years ago we had considerable experience with cholecystectomy without drainage, so that the opinion voiced here is not biased because of lack of trial of both methods. All of the cases herein reported were routinely drained unless the cholecystectomy followed a subtotal gastrectomy or other gastric operation. Such cases, of which there were 42 instances, were closed without drainage because it was believed that the presence of a drain might have a deleterious effect upon the gastric suture line. All the chronic cases had a cigarette drain placed down into the foramen of Winslow and all the acute cases had a gauze drain placed against the bed. The gauze was used in place of the cigarette because it was believed that gauze provoked a greater foreign body reaction and was more likely to cause a reversal of the lymph stream from the liver towards the bed, diminishing the tendency for absorption from the operative field (12). The cigarette drains were removed in 24 to 28 hours and the gauze drains were removed when the temperature dropped and the drainage diminished, which was usually at the end of 4 or 5 days.

Not infrequently following cholecystectomy, bile appears in varying quantities in the abdominal cavity. It may get there through accessory ducts to the fundus (13), tears in the liver bed, or cystic duct stump necrosis with leakage (14). It has long been known that large collections of bile may be found in the abdomen without any symptoms whatsoever but, on the other hand, occasionally the leakage of bile into the peritoneal cavity is responsible for a very rapidly fatal biliary peritonitis. In such cases the death may be due to two causes. Either anaerobic organisms come down with the bile from the liver where they have been quiescent, into the peritoneal cavity where they apparently become activated, or the action of the bile salts on the intestines which contain *B. welchii* induces permeability of the wall to these organisms so that they enter the peritoneal cavity. Because of such instances, even though they occur infrequently, it is

advisable to have a means of ready exit for such material from the peritoneal cavity. There is considerable experimental evidence favoring this viewpoint. Ellis and Dragstedt (15) demonstrated gram-positive anaerobes as responsible for the death of dogs into whose peritoneal cavities pieces of dog's liver had been placed. This is not true if sterile liver, obtained from

TABLE III
Complemental operations

Appendectomy	996
Gastro-enterostomy	21
Gastrectomy	15
Pyloroplasty	2
Excision of Perforated Pyloric Ulcer	4
Operation for Acute Pancreatitis	30
Partial Hepatectomy	5
Duodenostomy (for impacted stone in ampulla)	5
Closure of Colon (Cholecystocolic Fistula)	4
Closure of Duodenum (Cholecystoduodenal Fistula)	2
Resection of Colon (Hepatic Flexure)	2
Ileostomy (for Obstruction by Large Gall Stone)	1
Nephrectomy	9
Nephropexy	4
Excision of Cyst of Kidney	2
Hysterectomy	121
Salpingo-oophorectomy	67
Suspension of Uterus	52
Sterilization	62
Myomectomy	23
Cesarean Section	3
Umbilical Hernioplasty	30
Inguinal Hernioplasty	11
Femoral Hernioplasty	15
Incisional Hernioplasty	19
Trachelorrhaphy	27
Interposition Operation (for Prolapse)	7
Anterior Colporrhaphy	8
Perineorrhaphy	96
Hemorrhoidectomy	34
Excision of retroperitoneal cyst	1
Thyroidectomy	1
Total	1679

pups delivered by Caesarian section, is used. Andrews (16) repeating these experiments concluded that the liver was infected by *B. welchii* which passed through the intestinal wall. Rewbridge (17) and Andrews, Rewbridge and Hrdina (18) demonstrated that death was not due to presence of bile salts at toxic levels in the blood of dogs into whose peritoneal cavities bile was allowed to flow or sterile bile salts injected, but to a Welch bacillus infection.

In six cases which clinically simulated the almost invariably fatal syndrome described by many as due to "Liver-Shock," but which ultimately recovered, we were able to demonstrate anaerobic organisms of the Welch group in the biliary discharge from the drainage wound. On these grounds it is believed that our total mortality would have been considerably greater if routine drainage had not been employed.

MULTIPLE OPERATIONS

Much has been said about multiple operations, and usually without any factual basis. Our series offers considerable data on this subject. Reference to Table III reveals that the 1500 patients had 1679 other operative procedures performed. While the majority of these procedures (996) were appendectomy, there were still 683 other operations, some of which were of considerable magnitude or were performed for serious diseases and which of themselves carried a greater

operative risk than did cholecystectomy itself. For example, 22 of the 30 cases listed under operation for acute pancreatitis, which were reported upon elsewhere (19), had a mortality of 22.7%. A review of mortality statistics for acute pancreatitis shows a range between 22 and 78%. Since all but 5 of the 30 cases were treated by cholecystectomy, common duct drainage, exploration of the head of the pancreas, incision of the pancreatic capsule and drainage, it is far more likely that the mortalities were due to the pancreatitis and other procedures than to the cholecystectomy alone. Similarly gastrectomy carries a greater mortality than cholecystectomy in chronic cholecystitis.

Table IV, arranged to demonstrate the relation of cholecystectomy alone to cholecystectomy with other operative procedures, shows the greatest mortality to occur where the procedures were confined to the biliary tract alone. Thus, in 270 cases of cholecystectomy there were 29 deaths or 10.7%, and in 67 cases where operation was performed for common duct obstruction there were 9 deaths or 13.4%. The total of 337 cases showed a mortality of 38, or 11.3%. It is to be remembered that these cases were mainly those in which analysis has already shown that high mortalities were to be expected; i.e., where there was gangrene, perforation or common duct obstruction.

In the series in which appendectomy was performed after gall bladder removal, there were 710 cases with 25 deaths or a mortality of 3.5%. Obviously some of the gangrenous and perforated cases described under acute cholecystitis were included in this group, thus accounting for the high death rate.

TABLE IV

Classification	Number of Cases	Number of Deaths	Percentage Mortality	
Cholecystectomy	270	29	10.74	Total of 337 cases with 38 deaths
Operation for common duct obstruction <i>per se</i>	67	9	13.43	Mortality of 11.27%
Cholecystectomy and Appendectomy	710	25	3.52	Total of 710 cases with 25 deaths. Mortality of 3.52%
Cholecystectomy, appendectomy when present and other operative procedures	339	9	2.65	Total of 453 cases with 29 deaths
Cholecystectomy, appendectomy when present and operation for common duct drainage.	114	11	9.64	Mortality of 4.65%

Of greatest significance, however, are the results in the group of 339 cases in which cholecystectomy was done, the appendix was removed if present, and 683 other operations listed on Table IV were performed. In this group there were only 9 deaths, or 2.65% mortality. It immediately becomes apparent that any increase in mortality with multiple operations was due to the inherent mortality which the additional disease

or diseases (besides that in the biliary tract) contributed, and not to such factors as "additional exposure," additional anesthesia, or "too much surgery."

In the group of 114 cases in which cholecystectomy, appendectomy and common duct drainage were performed, there were 11 deaths or a mortality of 9.6%. Here again the inherently high death rate for patients with ailments for which the common duct must be drained is the factor in raising the mortality so much above that for simple cholecystectomy.

All this again raises the questions of what constitutes shock and how much can the patient stand. A yardstick to measure accurately the amount of injury any particular procedure offers and how much injury a particular patient could safely be subjected to, would solve the problem. The obstacles for its development are obvious since no two people are exactly alike, whether they be surgeon or patient. Thus the individual reaction to the problem will be varied. Some will say that what others now do routinely with good results is too much, and the latter group will scoff at the conservatism of the former. And yet both may be correct if they but point their arguments at themselves and not try to be crusaders. Thus, in the hands of a surgeon who would need an hour to do a cholecystectomy, Case 32020 discussed under the paragraph on spinal anesthesia, would probably never have survived all the other operations. And no pressure should be brought to bear upon such a surgeon to take upon

himself greater burdens than he feels he can handle.

It would seem that such surgeons need no other justification than that they tried to keep within "safe limits." It should be remembered, however, that general statements made by them about what is and what is not safe, may apply to them and not necessarily to all others. It is questionable, however, whether they should be allowed to set the standards. In this connection it might be worth while to quote from the paper by Stone and Owings (17—Acute Cholecystitis) "Standards of surgical treatment should be based on the course which offers the best results in competent hands. It is not sound policy to compromise principles of treatment to suit an assumed deficiency of skill in the medical profession."

We are presenting this material merely as one set of data on how much can be done and what the patient can stand. It is significant that similar statistical reports are conspicuously unavailable. To the possible criticism that too much surgery was done in these cases, we submit not merely the mortality analysis but also the acknowledgement of a distinct bias in favor of treating the patient as a whole rather than being "piece workers." Such an attitude conserves the patients' best interests by tending to diminish morbidity through recognizing and treating accompanying conditions and lessening the need for and danger from subsequent anesthetics, operations and post-operative convalescences.

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Primary Cancer of the Gall Bladder*

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PRIMARY carcinoma of the gall bladder is supposed by most clinicians to be a rare condition of interest only to pathologists. On the contrary, the disease, first described by Stoll in 1777, occurs with relative frequency. The present study amends an analysis of twenty-eight cases to the existing literature.

INCIDENCE

Figures from mortality, autopsy and surgical sources indicate an appreciable incidence of the disease. It is estimated that carcinoma of the gall bladder

ranks fifth to sixth in frequency in malignancy of the digestive organs, and is encountered in 0.4 to 0.85 per cent of all necropsies. Kaufmann (20) adds that the condition comprises five per cent of all cancers examined after death. In the tables of autopsy material compiled by Von Wolff and Bereney (2) from many authors, cancer of the gall bladder constitutes between 8.5 to 10.8 per cent of all carcinomata in women. Graham (14), from mortality statistics from the Bureau of Census, estimates that the disease accounts for eight to ten per cent of all carcinomas, and that its incidence for the general population is nine per one hundred thousand. Boyce and McFetridge (4)

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compute its surgical incidence to be 1.12 per cent in the course of 35,054 operations on the organ.

AGE AND SEX

Like gall bladder disease in general, carcinomatous involvement predominates in women. The present series of twenty-eight cases entails twenty-three females and five males in the ratio of 4.6 to 1.0, which is within the limits of the accepted average. Smithies (37) in all the literature appears to be the only dissenter. His series of twenty-three cases included sixteen males and seven females.

The youngest patient on record is a twenty-two year old male, described by Proescher (31). However, its authenticity is doubted. Rhodes and Greenblatt (33) cite a case in a twenty-four year old negress in whom calculi were absent. The oldest patient is apparently that of Illingsworth (15) who reported the disease in a ninety-five year old female.

Ewing (8) cites an average age incidence of 58 years. In the present study the highest incidence occurred in the sixth, seventh and eighth decades, the average age being 64.1 years. The average age of the male patients equalled 68 years, while that of the females was 62.4 years. The distribution in the various age groups were:

3 cases—5th decade
8 cases—6th decade
7 cases—7th decade
8 cases—8th decade
2 cases—9th decade

The youngest patient was forty-seven years of age, the oldest eighty-nine years.

It may be noted that carcinoma of the gall bladder has an onset later in life compared to cancer in general, and fortunately is a disease of advanced age.

ETIOLOGY

Considerable interest has been displayed in the causal relationship of cholelithiasis and cholecystitis to cancer of the gall bladder, engendering much speculation and also experimental study.

Calculi occur with appreciable frequency in gall bladders that are the seat of a malignant growth. The following table shows an incidence varying from sixty-two to one hundred per cent.

Judd and Gray	(18)	212 cases	64.6%
Janowski	(17)	40 cases	100.0%
Illingsworth	(15)	50 cases	62.0%
Futterer	(11)	209 cases	70.0%
Lentze	(25)	890 cases	83.0%
Musser	(28)	100 cases	69.0%

In the present series, 20 out of 28 gall bladders or 71.4 per cent, harbored calculi. It is conceivable that stones may have been present at some time in the eight stoneless cases.

The intimate relationship, moreover, may be viewed in a converse manner by observing the incidence of carcinoma in gall stone cases.

Fawcett and Rippman	(9)	592 cases	8.1% CA
Candler	(6)	315 cases	0.6% CA
Schroeder	(35)	141 cases	14.0% CA

As might be expected, females carried a higher incidence (Lentze).

The view has been espoused that the calculi may have formed in response to the neoplastic growth.

However, such idea is disavowed, but only inferentially, by the study of the incidence of stones in secondary carcinomata of the gall bladder. In Rolleston's (34) and Siegert's (36) combined series of twenty-six cases, calculi occurred only three times, while the incidence in thirty cases of Graham's (14) equalled eight per cent. Nevertheless, it may be noted that the occurrence of stones in secondary cancer of the gall bladder is well within the limit of incidence of cholelithiasis in general autopsy material.

To determine whether calculi may be an etiological agent in the pathogenesis of carcinoma, Kazama (21), in 1922, deposited foreign bodies including suture material, stones, etc., into the gall bladders of dogs, guinea-pigs and rabbits. In those containing the calculi, papillomatous formations and adenocarcinomata were found, and also what appeared to be metastases in the liver. Leitsch (24) subsequently confirmed the work of Kazama. However, Gioja (13) failed to duplicate the findings of the latter investigators. Burrows (5), in an experimental inquiry into the association of stones and primary carcinoma of the gall bladder, demonstrated that the mucosa of gall bladders containing implanted calculi undergoes marked proliferation even with penetration into the liver. Such sequence of events he defined as an example of cholecystitis glandularis proliferans, which hitherto had been misinterpreted as malignancy.

Ewing (8), from a pathological viewpoint, is of the opinion that precancerous changes are often pronounced in cases of cholelithiasis, which, by erosion, produce areas of atypical glandular epithelium showing numerous mitoses, evidently the beginning of carcinoma. Smithies (37) believes that no direct relationship between stones and cancer has been proved. Newman (29) feels on statistical grounds that both carcinoma and stones are due to cholecystitis, and not the cancer to stones.

The relationship of cholelithiasis to the carcinoma appears to be controversial. However, it may be pointed out that calculi in the same age group of the population occurs only in about ten per cent of cases, while its incidence in carcinoma of the gall bladder is about seventy per cent. Such variation in incidence appears to confer upon calculi some supporting etiological or intermediate role in the genesis of the neoplasm. Moreover, the etiologic role of gall stones is demonstrated by the striking preponderance of primary carcinoma in women. In addition, it is probably not the mechanical irritation of the concretions that acts as a direct cause of cancer formation in the gall bladder, but rather the chronic regenerative process accompanying it, coinciding with the age during which the organism displays a general disposition to cancer formation (Bottiger (3)).

The concept of chronic inflammatory cholecystitis as a precursor of malignant change finds much support and is believed to play a formidable role in the development of cancer of the gall bladder. Illingsworth (15) states that a pre-existing cholecystitis appears to be the invariable rule in the disease, and is one of the most perfect examples of a malignant growth arising as a result of chronic irritation. Ewing (8) adds that the scirrhus character of early growths of the gall bladder has a chronic productive inflammation as an antecedent factor. It is, however, of interest to note that in the series of carcinomata of the gall

bladder reported by Boyce and McFetridge (4) from the Charity Hospital of New Orleans, the incidence of the disease is practically equal among the white and negro races, whereas the ratio of cholecystitis in whites and negroes is 1 to 6 respectively. From this the inference that cholecystitis is not necessarily an etiological factor, may be drawn.

While papillomas do occur in the gall bladder, they are rarely believed to antedate a carcinomatous growth. Philips (30) records malignancy in only one of five hundred papillomata of the gall bladder, and even in this sole instance it was conjectural as to whether the neoplasm arose from a papilloma.

PATHOLOGY

The most frequent sites of origin of the tumor are at the fundus and neck of the viscus. In the majority of cases, the growth is so extensive that the original site cannot be determined, a condition prevailing in nineteen or 67 per cent of the present series. In only nine patients was the neoplasm sufficiently localized, four occurring at the fundus and five at the neck.

Carcinomata occurring at or near the neck frequently interrupt the continuity of the lumen of the gall bladder by contraction of its growth or by extension into the cystic and common ducts resulting in obstruction. Too, a relative stenosis of the neck by neoplasm may be completed by the secondary impaction of a calculus with associated inflammation and edema which occurred in one case. When the growth embraces the neck of the organ, symptoms accrue readily, and often cause an acute surgical picture. At operation the pathology may go unrecognized, simple drainage being instituted (*vide infra*).

The fundus is subject to irritation by stones by virtue of its dependency. Neoplasms arising at the fundus or along the lateral walls are more silent in their clinical expression and first become manifest when regional infiltration or metastases supervene.

Pathologically, carcinomas of the gall bladder may be classified into the adenocarcinomata and squamous types. The former may be subdivided into the papillary, the colloid or gelatinous, and scirrhous types.

Scirrhous Adenocarcinoma: This is the most common neoplasm encountered, and is represented in the present series by 15 or 53.5 per cent of the cases. The growth starts as a localized thickening or ulceration in the mucosa, and a notable feature is the associated proliferation of cellular connective tissue. The earliest type observed in the present study consisted of a hard indurated area, the size of an olive, situated near the neck of the gall bladder. It is interesting that even in such an apparent early stage a metastatic nodule was simultaneously present in the liver.

The growth progressively infiltrates and invades the organ and the walls become thickened and firm. The viscus may shrink extensively or contract to a rock-like consistency with obliteration of its lumen.

Involvement of the regional nodes and liver occur early, as witnessed by the above case.

Papillary Adenocarcinoma: This type occurred in 8 or 28.5 per cent of the cases. The tumor manifests itself as an abundant papillary overgrowth extending into the lumen of the gall bladder which it soon crowds and fills. The neoplasm is quite bulky and may reach extensive proportions. In one case, the growth appeared as a pedunculated and lobulated mass situated at the fundus.

Degeneration, necrosis and infection frequently supervene, and hemorrhage is not unknown. The walls then become soft and friable, and on section the organ appears black, grayish-green or yellow in color, and sometimes mushy and foul.

Colloid or Gelatinous Adenocarcinoma: There were three such neoplasms in the present study. The growth also is soft and bulky, and frequently reaches considerable size, the entire gall bladder being replaced by a soft caseous tumor mass. Early spread and extension to the neighboring organs is common.

Epidermoid Carcinoma: Epidermoid carcinoma, the least common variety of cancer of the gall bladder, was encountered twice. The growth transformed the organ into a firm mass with thickened walls, and in both acute infection supervened, one exhibiting an associated acute cholecystitis, empyema and suppurative cholangitis. The occurrence of squamous or epidermoid cancer is explainable only by a process of metaplasia from cylindrical epithelium of the mucous membrane. In one of the cases such transition could histologically be studied. The same specimen, most extraordinarily, revealed the presence of typical prickle cells and also cell nests of epithelial pearls.

MANNER OF SPREAD

Cancer of the gall bladder spreads principally by three routes—direct extension by contiguity, via the lymphatics, and by way of the blood stream. In addition, peritoneal transplantation does occur, and in the experience of Ewing (8), the sheaths of the nerve trunks have formed a frequent avenue of dissemination in his cases.

The gall bladder has a rich network of lymphatic vessels that anastomose with those of the adjacent hepatic surface and drain into the nodes about the cystic and common hepatic ducts. The lining also has an abundant submucous plexus of lymphatics (Sudler and Clermont (43)), and a profuse subserous network of vessels is also present.

The cystic and periportal nodes in the present series were most frequently involved, followed by those about the head of the pancreas and in the retroperitoneal tissues. In one case, spread to the retroperitoneal nodes was massive and conglomerate, and reached such proportions as to cause displacement of the duodenum and pyloric portion of the stomach anteriorly and laterally, with almost complete obstruction of the latter.

Neoplastic involvement of the nodes at the hilus of the kidney was twice observed. On one occasion, neither the trachea nor the esophageal nodes were spared. Involvement of the supraclavicular nodes has been reported.

Intimate association of the structures in the right upper portion of the abdomen permits extensive spread by contiguity. Moreover, the omentum and peritoneum become adherent to the organ-containing tumor in the early stages of growth, and thus serve as intermediate channels of dissemination.

The liver suffered most consistently and extensively from neoplastic invasion, and was involved in twenty-three or 82.5 per cent of the series. In the five remaining cases, metastases were judged to be absent only grossly. In the majority of cases, hepatic involvement was of the disseminated variety, from one to numerous nodules studding the entire organ. Direct

infiltration of the liver was also observed. The entire quadrate lobe was twice replaced by tumor tissue, and in one instance, almost the entire right lobe was directly and massively infiltrated.

By contiguity, the growth spreads along the cystic and into the common hepatic duct, occasionally into the hepatic duct, and has even been described to extend into the liver in this manner. The cystic and common ducts are often partially or completely occluded by neoplastic tissue, filling their lumen or infiltrating their walls and periductal structures.

By direct spread, the stomach and duodenum may be invaded, even down to the mucosa, and in one case such invasion precipitated a massive gastric hemorrhage. Nodules were found in the transverse mesocolon, in the wall of the transverse colon, and on two occasions the pancreas was extensively infiltrated, causing displacement of the duodenum laterally. Pea-sized nodules in one case were found invading the wall of the inferior vena cava; nor was the portal vein exempt in two instances.

Peritoneal involvement, a frequent occurrence, was twice sufficiently extensive to cause a fatty (chyli-form) type of ascites as a result of cellular degeneration of the secondary growths.

Via peritoneal transplantation nodes were found in the sigmoid and in the serosa of the Fallopian tubes.

Spread by way of the blood stream does occur directly or via the portal system. The skeletal system is usually spared by biliary carcinoma. However, in one case, pathological fracture with collapse as a result of metastases occurred in the first lumbar vertebra. Beadles (1) has reported a case with metastasis to a rib. Involvement of both adrenals occurred twice, one gland being entirely destroyed by cancerous tissue. Warthin (40) has cited a case of carcinoma of the gall bladder with extensive destruction of the adrenals, causing adrenal insufficiency and simulating Addison's disease.

The pleura and both lungs were studded with tumor nodules in two cases. One kidney and one ovary revealed parenchymatous involvement. Curiously enough, metastases to the spleen occurred in one case.

PAST HISTORY

A relevant past history was elicited in ten (34 per cent) cases, ranging from 3 to 30 years, and varying from vague dyspepsia to well-defined attacks of biliary colic. It is significant that five patients were perfectly well prior to the onset of the present illness, and when hospitalized had been ill for 22 days, 2 months, 6 months, 6 months and 7 months, respectively.

CLINICAL PICTURE

It may be stated peremptorily that there are no pathognomonic signs or symptoms distinctive of carcinoma of the gall bladder. Lancereaux (23) symptomatically divides the disease into a biliary form featuring dyspepsia, an abdominal mass, jaundice and pyrexia; and an hepatic form in which a rapidly enlarging liver is the salient finding. Rolleston (34) distinguishes three classes of symptoms: those associated with a pre-existing cholelithiasis; those arising because of regional and distal spread; and the local effects of malignant disease.

The present series of cases may be divided into five classes in terms of the presenting clinical picture and in the light of the many miscellaneous diagnoses that were originally suggested. In such manner the protean manifestations of the disease and its differential diagnosis may be jointly illustrated.

1. The first and most common group of patients fitted into an obviously malignant picture, clinically. The primary sites suggested to the clinician in order of frequency were: stomach, large bowel, pancreas, gall bladder, kidney and ovary. A correct diagnosis of cancer of the gall bladder was made only once. In three cases it was merely one of the several diagnoses mentioned.

2. In this class of patients a diagnosis of chronic cholecystitis with or without lithiasis was made most constantly. An associated common duct stone was suggested in one-half of these cases. Pain in all its variations was the outstanding symptom. Occasionally groups one and two overlapped.

3. Four patients presented a picture of an acute surgical nature, consisting of severe right upper abdominal pain, marked tenderness, muscular rigidity, and associated chills and fever. The preoperative diagnosis in all cases was acute cholecystitis and cholelithiasis with empyema of the gall bladder. It is interesting to note that in three of the patients a diagnosis of carcinoma was first made histologically, the signs of infection and inflammation evidently overshadowing those of neoplasia. In the fourth patient, an operative diagnosis of subhepatic abscess was made, without suspecting malignancy of the gall bladder.

4. Two patients simulated a clinical picture of portal cirrhosis with marked ascites that required frequent paracentesis.

5. The last group comprised two patients that sought hospitalization because of a symptomless right upper quadrant mass. In three cases, carcinoma of the gall bladder was an incidental finding at necropsy, the patients dying of congestive heart failure, caseous pneumonic tuberculosis, and as a result of an automobile accident, respectively.

The major signs and symptoms may be more fully analyzed as follows:

Pain

Pain was the most frequent and constant symptom, present in 19 (67 per cent) cases, in 17 of which calculi were an added finding. The pain ranged from a mild right upper quadrant and epigastric distress or ache to a severe and prostrating colic with associated nausea, vomiting, and radiation to shoulder and back, indicating a peritoneo-cutaneous type of distribution. The pain was either constant, remittent or intermittent in rhythm. If pain had been present in the past history of the individual, it now dominated the clinical picture by its greater intensity, constancy and frequency.

Mass

A definite palpable mass was noted in 17 (60 per cent) cases. The mass was usually described as firm, of an irregular outline, and more often than not, with associated tenderness. When the growth was not bound down by adhesions or regional infiltration (6 cases), it moved in the phases of respiration and was

ballotable. In 2 cases, the neoplastic mass was prominently visible.

Ascites

Appreciable ascites was evident in 6 cases, and in two was massive and of a chyliform nature.

Jaundice

Jaundice occurred in 13 (46 per cent) cases. In 4 it was present at the onset, and in one case was the sole complaint. In all patients, except one, the jaundice was progressive. In the latter, intensive jaundice disappeared because of spontaneous formation of a cholecyst-duodenal fistula (vide infra).

The icterus was, in all cases, obstructive in type and due to occlusion of the common duct by malignant infiltration, or by compression of the duct by neoplastic nodes or cancerous quadrate lobe. In not a single instance was a calculus found in the extra-hepatic ducts. Once jaundice made its appearance, life expectancy was very short.

Weight Loss

Loss of weight was a prominent symptom and occurred in 18 (64 per cent) cases. The loss of flesh was not a gradual decline, but usually a rapid fall. One patient, who hitherto had been in robust health, lost sixty pounds over a period of five months. The average weight loss ranged between fifteen to twenty-five pounds. Rehfuß (32) states that after an acute gall bladder attack there may be a pronounced weight loss, especially if pancreatic disease is concurrently present. He further adds that continued weight loss associated with upper abdominal indigestion, particularly during middle age, should give rise to a suspicion of malignancy of the stomach, pancreas or colon. A noteworthy addition as a primary site of cancer is certainly the gall bladder itself, and it deserves to be stressed.

COMPLICATIONS

Infection and acute cholecystitis may supervene in the carcinomatous gall bladder and proceed to empyema, perforation, local abscess formation and suppurative cholangitis, and regional or general peritonitis. Such train of events occurred in seven patients, the pathology of which is succinctly outlined.

1. Malignant lesion near the neck of the gall bladder in which a stone was impacted. Lumen filled with two ounces of thick purulent material. The cystic duct was absolutely occluded by malignant tissue.

2. Gall bladder surrounded by many dense adhesions. Incision into its wall revealed contents of heavy thick purulent material with stones. At post-mortem the biliary ducts were dilated and filled with pus. Multiple liver abscesses were present.

3. Gall bladder enlarged, walls thickened and edematous, and contained a few centimeters of thick pus. A perforation was present two inches above the fundus into the liver bed forming an abscessed cavity containing about 250 cc. of thick yellow creamy pus. Another perforation was present anteriorly, and sealed off by omentum. Many stones were present.

4. Thick-walled gall bladder containing stones, pus and a walled-off perforation with abscess formation. A stone impacted the cystic duct.

5. Hard mass surrounded by many dense adhesions and omentum. Mucosa was dark red and hemorrhagic. A perforation was present in the fundus with a stone protruding.

6. Soft, friable, necrotic mass about and communicating with gall bladder. Pus exuded on pressure. Many stones present.

7. Necrosis, dissolution and perforation of the malignant gall bladder wall, which, with the adjoining organs, formed a grayish, green, foul and gangrenous mass in the upper abdomen. Generalized peritonitis with pockets of pus between the intestinal coils. Calculi were present.

Thus there were seven cases of concomitant empyema of the gall bladder. Five had perforated, in one of which suppurative cholangitis and multiple hepatic abscesses were also present, and another resulted in generalized peritonitis. It is interesting to note that stones were present in all cases. In four of the cases that came to operation, the surgeon did not suspect a malignancy to be present.

An unusual case of cholecyst-duodenal fistula formation occurred, presenting an interesting clinical picture, and meriting a brief account.

A seventy-five year old female complained of constant aching epigastric and right upper quadrant pain of six months duration, with associated nausea and vomiting. There was a weight loss of twenty pounds. Six months subsequently, jaundice appeared and soon deepened markedly. On examination, a large mass was present in the right upper quadrant and right loin. A nodular liver was palpable three finger breadths below the costal margin. Flatplate of abdomen showed many stones in the gall bladder region. Six days before death, the patient experienced a massive hematemesis and subsequent tarry stools, after which the jaundice rapidly declined. At necropsy, the gall bladder wall was thickened and composed of friable white tissue, which extended without a line of demarcation into the surrounding liver. The lumen contained yellowish necrotic tissue. On the right lateral wall of the descending duodenum, a round ulcer was found. The edges were not undermined, and the base consisted of a necrotic, yellowish-white tissue, through which a fistulous tract extended into the lumen of the gall bladder posteriorly. Histologically, the fistulous tract was lined by numerous islands of neoplastic cells. Several groups of tumor cells invaded the wall of the duodenum. The common bile duct was practically devoid of lining epithelium, its wall was fibrotic and surrounded by numerous tumor nodules. Many stones were present in the gall bladder.

DIAGNOSIS—TREATMENT—PROPHYLAXIS

It must be confessed that an accurate diagnosis of cancer of the gall bladder in its early stages is really a happy guess, and is most often attendant upon the development of cachexia or evidence of metastases. The gall bladder is not a vital or essential organ. Cancer growth may progress uninterruptedly and extensively before there is clinical expression of its presence. A mass in the right upper quadrant with associated pain, particularly in a woman in the seventh to eighth decade exhibiting significant weight loss and radiographic evidence of calculi, should suggest the diagnosis. However, such criteria do not embrace all

cases and merely recognize the advanced phases of the disease.

Even at the operating table, the pathology may be masked by an associated acute inflammatory process such as occurred in four of the present cases. Surgeons evidently must be more alert to detect its presence, and mindful that behind an acute surgical condition in the gall bladder, cancer may be lurking; and also that malignancy may develop in a gall bladder that had been previously subjected to cholecystostomy.

Cholecystography has not materially assisted in the diagnosis, the customary finding being a non-visualized gall bladder, borne out by the present study. A flat plate revealed calculi in only six instances. Taterka (39) reported one case in which there was a filling defect of the outer wall and an indentation of the inner wall of the gall bladder, following the Graham Test.

Kalk (19) believes that laparoscopy is justified to exclude the suspicion of cancer of the gall bladder, which he has seen repeatedly. Such procedure, while useful in visualization of lesions about the fundus and of metastatic nodules in the liver, will not detect early neoplasms about the neck of the gall bladder.

The difficulties in diagnosis obviously portend a gloomy prognosis. The average duration of life in nineteen patients who had died equalled 4.47 months from the onset of what apparently was the present illness, certainly an abbreviated course. Sixteen cases came to operation. In eight, the abdomen was systematically opened and closed. In six cases, cholecystectomy was performed; one died post-operatively in pulmonary edema; two succumbed after six months; one patient is living one year later with inception of severe jaundice and little life expectancy; one patient, who had an additional choledochotomy is living seventeen months; another, who had a cholecystostomy one and one-half years previously, has not been heard from. In two patients, cholecystostomy was performed; one is living one and one-half years later; the other died six months subsequently of multiple liver abscesses.

Rhodes and Greenblatt (33) report one patient living after five years. Gibson (12) reports 100 per cent mortality from the New York Hospital, and Stout (38) has had the same experience at the Presbyterian Hospital in New York. In Smithies series, 21 patients died immediately or within eight months of operation. However, Magoun and Renshaw (27) report seven cases which were living five years post-operatively, and Webber (41) cites twelve cases which survived more than two years.

It appears that carcinoma of the gall bladder is necessarily a fatal disease, unless the growth can be removed by surgical extirpation, a procedure usually not feasible because of the extent of the disease, when it reaches the hands of the surgeon. Such arguments are used by the exponents of prophylactic surgery, who would remove all gall bladders containing calculi in patients within the cancer age. Graham (14), who considers gall stones as a definite precancerous lesion, contends that four to five per cent of women within the cancer age with calculi will develop cancer of the gall bladder. His operative mortality from cholecys-

tectomy is 1.5 per cent, which is about one-fourth of the danger of developing cancer, and he further states, "From the standpoint of cancer prevention, it would seem our duty to inform patients with gall stones, that in general, they have a greater chance of dying from carcinoma of the gall bladder than they would have by a properly performed operation." In view of the almost hopeless outlook for patients with carcinoma of the gall bladder, such argument does not lack recommendation. However, it is probable that if such a view point were generally adopted, the mortality from cholecystectomy would likely exceed the incidence of the disease. Moreover, as Eliason and North (42) have pointed out, the incidence of carcinoma of the gall bladder (estimated to be one to two per cent of all cases of diseases of the gall bladder and its ducts) is less than the mortality of the best elective cholecystectomy, and the removal of silent stones cannot therefore be urged on the grounds of their threat to the development of cancer.

CONCLUSIONS

1. Carcinoma of the gall bladder occurs more often than is commonly supposed; predominates in women, and is more prevalent in the later decades of life, the average age of the present series being 64.1 years.

2. Opinion is disposed to view calculi as a source of irritation, and in conjunction with inflammatory cholecystitis, to play a role in the genesis of the growth. Stones occurred in 71.4 per cent of the cases reviewed.

3. The fundus and neck of the viscus are the most frequent sites of origin. Pathologically, the series consisted of 15 scirrhous, 8 papillary and 3 colloid adenocarcinoma; and 2 epidermoid carcinomas. In one of the latter, typical prickly cells and nests of epithelial pearls were present.

4. Carcinoma of the gall bladder spreads principally by contiguity, the lymphatics, by way of the blood stream, and also via peritoneal transplantation. The liver is most frequently implicated by secondary growths. Despite the rarity of skeletal involvement, metastases occurred to a lumbar vertebra. Splenic metastasis was observed once. Other sites of spread have been described.

5. The cases have clinically been divided into five groups: one with evident clinical stigmata of malignancy; another with signs and symptoms apparently that of cholecystitis and cholelithiasis; two cases simulated portal cirrhosis; an important group that presented an acute surgical picture; and a final group with sole complaints of symptomless right upper quadrant mass, or in whom the neoplasm was an incidental necropsy finding.

6. Pain was the most frequent and constant symptom, and was present in 67 per cent (19) of cases, in 17 of which calculi were associated. A mass was noted in 60 per cent of cases, and jaundice, of the obstructive type, in 46 per cent. Rapid weight loss was a significant finding.

7. The cases have been characterized by a high incidence of surgical complication, the pathology of which has been outlined. Acute suppurative cholecystitis and empyema supervened in seven cases, five gall

bladders of which perforated with subsequent regional or generalized peritonitis. One patient developed a spontaneous cholecyst-duodenal fistula.

8. Operative results have been ominous, only one of sixteen cases submitted to surgery presenting a possibility of cure. Carcinoma of the gall bladder is

an insidious disease, eludes early diagnosis, and is usually recognized in its later stages, when surgical extirpation is not feasible. Prophylactic removal of gall bladders containing calculi has been advocated.

9. Possibility of the presence of cancer of the gall bladder is emphasized both to surgeons and clinicians.

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Clinical Study of a New Synthetic Spasmolytic Drug: Diphenylacetyl-diethylaminoethanol*

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RECENTLY we have reported on the pharmacological properties of Diphenylacetyl-diethylaminoethanol (for shortness called "T") (1). Its marked spasmolytic properties, combining those of atropine and papaverine, encouraged us to try this drug on a variety of pathological conditions in man. While we found that T is no panacea for all spastic or painful symptoms of the gastro-intestinal tract, such striking positive results were obtained in a number of conditions, that we feel justified to publish this report. It substantiates favorable reports from abroad (2) and from this country (3), and adds new observations of our own.

Our subjects were patients from the free medical clinics and from the wards of Michael Reese Hospital and a few private patients. T was administered by mouth or by hypodermic injections. The optimal dose

by mouth was found to be 150 mgms. (2 pills each of 75 mgms.) usually given 30 minutes before meals; by subcutaneous injection 75 mgm. (1 ampoul). All cases reported were controlled with other methods of therapy. Case reports will be given only to illustrate typical and interesting conditions. Negative findings are not reported.

RESULTS

A group of 12 patients with gastric or duodenal ulcer, two patients with marginal ulcer following subtotal gastrectomy, 12 patients with hypertrophic gastritis, and 9 patients with irritable colon were treated with T. In these three groups beneficial effects were obtained, but in no higher percentage than with other methods of therapy, and therefore the cases will not be discussed in detail. We want to state, however, that T produced relief or improvement in a number of cases, in which the usual therapy, that is diet, alkalies, bismuth and atropine, were not of much help.

*Supplied by the Ciba Company under the trade name of Trasentin.

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‡Michael Reese Hospital, Chicago, Ill.

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Two patients suffering from disturbing symptoms of biliary dyskinesia following cholecystectomy for stones and one patient suffering from cholelithiasis, obtained temporary relief with T while ordinary therapy was of no avail. After six weeks of medication T was discontinued while the patients were advised to be careful with their diet. Occasional upsets, which occurred usually with dietary indiscretion, are being successfully treated with T.

The last group represents five cases of great interest, to be discussed in detail. All of them suffered from intractable diarrhea, due to a great mechanical interference with normal function of their intestinal tract.

Case 1* is a white man, 21 years of age. A few days after recovery from the resection of fifty inches of ileum caught in an internal hernia, he began to have 10 to 20 watery stools a day. The diarrhea could be reduced only with paregoric, and kept up at 5-10 diarrheal stools per day for 7 months in spite of various forms of treatment including diet and atropine. X-ray examination showed a hypermotility of the bowel. No parasites or ova could be found in the stools. On giving 75 mg. of T t.i.d. before meals the diarrhea immediately stopped and has returned only when no T was taken for 2 days. During the following month the patient was able to reduce the dose to 2 tablets in 3 days (50 mgms. per day). He has 1-2 bowel movements per day; the first one, in the morning, is of normal consistency and appearance, the second one soft, but formed. He has been gaining weight steadily and three months after beginning of taking T has been working full time which he had been unable to do since his operation.

Case 2 is a white man, 42 years of age. In February, 1938, he was operated for intestinal obstruction, and a carcinoma of the jejunum was resected. A cecostomy had been made previously. Nine days after operation oral feeding was begun. The discharge from the cecostomy increased, and became watery and brownish, containing food eaten shortly before, and was more or less continuous. Five days afterwards, medication of T, 150 mgms. t.i.d., 30 minutes before meals, was started. On the second day of this regime, the amount of drainage from the fistula receded considerably; the third day a moderate amount of soft, light brown fecal material was discharged through the fistula; nine days later, small brown soft stools were evacuated, and from 2 weeks on after the beginning of medication, 1-2 formed brown stools were evacuated daily through the cecostomy. The patient gained considerable weight, and was out of bed and went home to recover for closure of the fistula.

Case 3 is a white man, 22 years of age, in whom four weeks after the closure of an ileostomy (terminal ileitis, resection of lower ileum) an ileal fistula had formed, which discharged large amounts of fecal, fluid material. Therefore, two days after beginning of this discharge and considerable dehydration of the patient, administration of T was begun. In view of the great loss of fluid and food through the fistula, T was injected s.c., 75 mgms. (1 ampoul) t.i.d., 30 minutes before meals, and once at night. On the second day of medication the volume of discharge from the fistula diminished considerably and was of soft consistency. Three days later, the discharge was moderate, partly soft and partly liquid, usually 3 times per day. At that time, oral administration of T was started, 2 tablets (150 mgms.) of T being given t.i.d., 30 minutes before meals. Three days later, small amounts of formed stools were evacuated twice daily from the fistula; 5 days after this the ward ran out of T and the patient did not get any for one day; large liquid stools appeared. The next

day T was available, and from then on a formed fecal discharge from the fistula occurred once to twice daily.

Case 4 is a white man, 42 years of age, in whom an ileal fistula developed following closure of an ileostomy done after resection of a carcinoma at the ileo-cecal junction. A considerable discharge of semi-liquid stools began from the fistula. Following our previous experience, medication of T was given immediately: two tablets (150 mgms.) per os t.i.d., 30 minutes before meals. From the second day on of this regime moderate amounts of soft, formed stools were discharged from the fistula.

Case 5 is a white woman, 19 years of age, in whom after appendectomy, oophorectomy and salpingectomy and later colpotomy, two fecal fistulas had formed; one from the appendectomy wound, and the other from the vagina. July 12 the patient was emaciated and dry due to constant and considerable loss of fluid from both fistulas, and undigested food from the upper one. Septic temperatures and parotitis developed. She had been given soft, bland diet, and transfusions of blood and glucose. Seventy-five mgms. of T was administered subcutaneously five times per 24 hours. Within two days the watery discharge from both fistulas diminished. T was given per os from now on, 150 mgms. (2 pills) t.i.d., 30 minutes before meals. On August 1, the patient looked and felt much improved; the diarrheal discharge was diminished markedly; the abdominal fistula was cleaning up and granulating. September 24, little discharge from both fistulas; patient out of bed. She has gained weight and strength and was sent home to recover more for surgical closure of fistulas.

DISCUSSION AND CONCLUSIONS

While T did not offer relief to all patients studied suffering from ulcer or irritable colon, it was of value in a number of cases, in which orthodox therapy failed. It may therefore, be useful and worthy of trial in the cases of such patients refractory to diet, alkalies, sedatives and belladonna.

In two cases of hypertrophic gastritis one patient who derived some but not complete benefit from the usual therapy, was completely relieved of all symptoms by T, while the other patient showed some improvement. The group of 3 patients with disease of the biliary tract is small, but the results warrant further trial on similar cases. A patient suffering from cholelithiasis was relieved while taking T, while the usual regime of diet, alkalies, atropine, etc., did not offer much or any relief. The same was true in two cases of biliary dyskinesia, both after cholecystectomy for stones.

In our study on the pharmacology of T we have found (1) that this drug exerted a powerful relaxing effect on the gall bladder, a fact which we have confirmed in normal, unanesthetized dogs (4). We assume, that a similar relaxing effect is exerted on the bile ducts and on the sphincter of Oddi. We know besides that the small intestine is relaxed effectively following T (1), and consider this essential for evacuation of bile through the sphincter of Oddi (4).

The last group of patients (1-5) represents the most spectacular results, because in each of these T offered complete relief in abolishing a diarrhea which was refractory to usual therapy, although opiates afforded relief in one case.

In Case 1 in which the greater part of the ileum had been resected one must assume that the motor, absorptive, and secretory mechanisms of the remaining intestine were upset; besides, a change in the intestinal bacterial flora is likely to occur and contribute

*We wish to thank the members of our surgical staff for the permission to administer T to some of their patients.

as disturbing agent. In this subject and to a less degree in No. 2-5 a disturbance of the normal intestinal gradients (Alvarez (5)) may be considered to be an important factor in the greatly increased motility of the intestinal canal. We know from experiments on anesthetized and normal dogs, that small and moderate doses of T decrease tonus and motility of the gastro-intestinal tract, but do not abolish them (1). We have reason to believe, therefore, that the beneficial effect of T in the above cases is due to a slowing of intestinal motility and lowering of tonus with restitution of a more normal intestinal gradient. The change in these patients from watery diarrhea to formed stools, their gain in weight, strength and appearance certainly favors such assumption. The checking of the diarrhea increased the digestive and absorptive capacity of the intestine. The colon below the abdominal fistulas in Cases 3-5 was equally affected and the stools from the rectum and vaginal fistula in Case 5 were firmer and more normal. We know that fistulas of the ileum, cecum, or colon have a variable clinical course, and that they may improve and even close with or without drug therapy. We do not claim that T had any specific effect on the healing of the fistulas described, except by the stopping of diarrhea and watery discharge from them. The latter effect was dramatic and beyond question. In the beginning of medication of T when the diarrhea had stopped, immediate recurrence of it occurred when T was omitted, and soon stopped after it was given again. In Case 1 (resection of ileum) constipation was not observed at any time.

A few side reactions were observed. One was dry-

ness of the mouth which was reported by two women. This seems to be a rare occurrence. Members of this laboratory have tried T on themselves on many occasions and never observed any dryness; in acute experiments on dogs a slight reduction of submaxillary salivary secretion was noted, but never complete abolition as with comparable doses of atropine (1). Two patients who received subcutaneous injections of T complained about painful swelling at the site of injection, which subsided however, without abscess formation. We feel that this swelling may have been accidental, i.e. rather due to contamination at the site of injection than to the drug. In conclusion we want to state, that while T is not a panacea for all spasmodic conditions of the gastro-intestinal tract, it is a valuable aid in a number of conditions in which usual therapy is unsatisfactory and that it seems to be invaluable in the treatment of postoperative diarrheas.

SUMMARY

A synthetic drug, Diphenylacetyldiethylaminoethanol (Trasentin) has been tried on 32 patients. It was helpful in a number of cases of duodenal and marginal ulcer, gastritis, cholelithiasis, biliary dyskinesia and spastic colon in which usual therapy was of no or little help. In five patients it stopped postoperative diarrhea which was refractory to usual medication except paregoric. We therefore feel Trasentin is of value and has a place among the effective antispasmodic drugs, and that it may be invaluable in the treatment of diarrhea in the case of intestinal fistulas and after operations which shorten the small intestine and may upset its normal gradients.

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Gastro-Intestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin*

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DODDS (1934) and others have shown that high doses of the pressor principle of the posterior pituitary may produce a severe gastritis with subsequent ulcer formation in various laboratory animals

(1, 2, 3). Pitressin reduces the blood flow through the stomach (4) and depresses gastric secretion (5, 6). Acetylcholine (a.c.) is liberated by efferent impulses at the endings of the vagus nerves in the stomach and afferent impulses in the vagi apparently cause an output of pressor substance from the posterior pituitary (7, 16). Small doses of a.e. constrict the blood vessels of the canine and human stomach

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and may thereby produce gastric ulcers (8-13). A.C. is a potent stimulant for gastric acid secretion (14). Besides gastric lesions following administration of pitressin, Dodds and collaborators (15) described a progressive anemia which they could not explain by hemorrhage in the gastro-intestinal tract, but by some disturbance in normal blood formation. They found a blood picture somewhat similar to that in pernicious anemia and greatly diminished volume of gastric juice, but with little change in its acidity. They used single doses of six to eight hundred pressor units of posterior pituitary extract. Since such high doses are far beyond physiological limits, we tried the effect on the gastro-intestinal tract of dogs of smaller doses of pitressin given by constant injection; in other experiments one afferent vagus was stimulated in order to effect reflex liberation of pressor substance from the posterior pituitary (7, 16); besides, constant injection of a.c. was also tried. The bearing of such experiments on the problem of the neurogenic origin of gastritis, colitis and peptic ulcer requires no discussion.

METHODS

Unanesthetized dogs were submitted to constant intravenous injection of (1) a.c. (2) a.c. + pitressin† (3) pitressin and (4) stimulation of the central end of the right vagus nerve (7, 16).

In all dogs receiving constant injections, the external jugular vein was cannulated under light ether anesthesia. The cannula was connected by a rubber tube to a large burette and the flow of the solution controlled by a screw clamp.

(1) Acetylcholine: Three dogs received a continuous injection for 28, 31 and 51 hours. Another three dogs were injected only during the daytime for 3 to 6 days with a total injection time of 18 to 37 hours. This last group was fed every evening; the first group did not get any food by mouth and was starved 24 hours before the experiment, but in experiments of longer duration the dogs received glucose intravenously for nutrition. The concentration of a.c. was from 20 to 400 gamma per cc. of saline and the total amount administered varied between 61 to 1200 mg. of a.c.

(2) A.C. + Pitressin: Two dogs were infused, during daytime only, and fed every evening. The experiments lasted three and six days with a total infusion time of 21 and 33 hours respectively. The concentration was 10 mg. a.c. + 1 pressor unit pitressin per 100 cc. of saline for one dog, and 10 to 20 mg. a.c. + 1 to 2 pressor units pitressin per 100 cc. of saline for the other. The total amounts received were 214 mg. a.c. + 21.5 p.u. pitressin and 700 mg. a.c. + 70 p.u. pitressin, respectively; i.e., approximately 10 mg. a.c. + 1 p.u. pitressin per hour in the first dog and 21 mg. a.c. + 2 p.u. pitressin per hour in the second dog.

(3) Pitressin: Ten dogs were used. The experiments lasted from 2 to 8 days; the dogs were injected for a total of 10 to 53 hours during daytime only, and were fed in the evening. The concentration of pitressin ranged between 1 and 8 p.u. per 100 cc. of saline and the total amount received between 25 and 150 p.u. (8 dogs) pitressin; one dog received 280 p.u. over five days. On the fifth and sixth day of the experiment, two dogs of this series received an enema of a freshly prepared culture of *Bargen diplococci*.‡ One dog received 4 to 5 p.u. pitressin subcutaneously in hourly intervals for 22 days (during day-

time). The total amount was 600 pressor units; on the 20th day he received an enema of *Bargen's diplococci*.

(4) Central Vagus Stimulation: Five dogs were used; under pentobarbital sodium or ether anesthesia the right vagus was cut in the neck and silver wire electrodes attached to its central stump. The electrodes were well insulated and the wires brought through the skin of the neck and connected to the secondary coil of a Harvard inductorium with two dry cells in the primary circuit. The experiments lasted from 4 to 10 days with one hour stimulation and fifteen minutes rest alternating. The distance of the secondary coil of the inductorium varied between 11 cm. in the beginning and 4 cm. toward the end of the experiment. The dogs received food every evening and rested during the night.

At the end of the experiments all dogs were put to death rapidly and painlessly. Five died during the course of the experiment.

RESULTS

All dogs were autopsied immediately after death.

Group I. Acetylcholine only. Three stomachs showed grossly definite gastritis: the mucosa was inflamed, its folds swollen and edematous and covered with a thick greenish and yellowish mucoid material which could be removed with difficulty only. After removal of this mucus hemorrhagic gastritis with or without erosions was seen. In some stomachs six to ten pinpoint mucosal hemorrhages were present. The changes in the small intestine were similar. They were mostly localized in duodenum and jejunum, decreasing in number and degree towards the cecum. The lesions found in the duodenum were much more severe than those of the stomach and mucosal erosions with a diameter varying between 2 and 20 mm. were observed in two dogs. The duodenum showed diffuse inflammation throughout; in jejunum and ileum inflammatory processes were observed more or less localized around the lymph patches. The colon was normal.

Group II. Acetylcholine + Pitressin: Pathological findings were similar to those of Group I, but in addition the colon was found to be filled with bloody mucus and fresh blood. The mucosa had lost its normal color and appeared hyperemic and dark red, especially on the crests of the folds which besides were edematous and swollen.

Group III. Pitressin: The same pathological picture was seen as in Group II but in a much more severe form. Beginning immediately behind the ileo-cecal valve the entire colonic mucosa was involved. In 7 out of 10 cases there was a grossly moderate or severe hemorrhagic and ulcerative colitis. Most of the fresh blood which filled the colon undoubtedly came from ruptured capillaries of the engorged mucosa, or from small bleeding erosions. The folds were swollen and covered with bloody gelatinous mucus.

Microscopically, most of the specimens of stomach and intestines showed a marked hyperemia of the mucosa with engorgement of the capillaries and small focal hemorrhages. There was cloudy swelling and a considerable hypertrophy of the lymph tissue in the colon. However, it must be stated that the microscopic findings were in contrast to the definite microscopic and clinical picture. No deep ulcers with arterial bleeding were found as would have been expected in animals that suffered from gross gastric and intestinal

†Liberal supplied by Dr. Oliver Kamm, Parke, Davis & Co.

‡We are obliged to the Department of Bacteriology for supplying the suspensions.

*We are obliged to Drs. Corrigan and Appel from the Department of Pathology for help with the histologic examinations.

hemorrhage. The toxic effect of pitressin in the doses employed seems to produce mainly engorgement of the capillaries of the mucosa of stomach and intestines and especially of those of the ileum and colon. Many of these capillaries break, thus producing diffuse superficial hemorrhage.

Group IV: Stimulation of right central vagus. We found a medium degree of hemorrhagic condition of the upper part of the gastro-intestinal tract resembling the findings in animals that had received infusions of a.c., but for technical reasons it was not possible to reproduce these pathologic changes with such regularity as in the other groups.

The general pathological findings correspond to those described by previous authors (17-19), who employed different methods of administration and larger doses of the drugs. Dogs which had received acetylcholine showed subserous petechiae in the lungs and congestion of liver and pancreas. Similar observations were made in dogs which had received pitressin; in addition, they showed infarction and fibrosis of the kidneys, and enlargement of Malpighian corpuscles and large deposits of hemosiderin in the spleen.

DISCUSSION

We believe that the concentration of acetylcholine reaching the gastro-intestinal tract was rather small; besides the factor of dilution, rapid destruction of the ester occurs in blood and tissues (20). The dosage of pitressin was relatively higher, certainly greater than that occurring normally. It was small, however, compared to the amount employed by previous authors (1, 2, 3, 15), and we feel that much smaller concentrations of pitressin infused over long periods of time would be equally effective. Besides we believe that an individual susceptibility of the experimental animal to pitressin plays a rôle in the occurrence of the pathologic changes observed because no definite relationship could be found between pathologic findings and doses per kilogram of body weight and duration of injection. We know that ischemia of the stomach,

focal or general, may under certain conditions produce inflammation and ulceration (1, 13, 21). Both, a.c. and pitressin, are known to cause vascular contraction in stomach and duodenum. Pitressin is known to produce arteriolar contraction in general. We are not in a position as yet to explain the greater affection of ileum and colon by pitressin, and the prevailing effects of a.c. on stomach, duodenum and jejunum. We have shown that a pharmacologic relation exists between a.c. and pitressin, the latter inhibiting the vaso-depressor effect of a.c. (16), but this does not seem to be related to our present problem.

Stimulation of the central vagus apparently did not cause an appreciable output of posterior pituitary principle. It must be remembered, however, that in such long lasting experiments one is not always certain whether living vagus nerve is being stimulated by the current. The changes found in the upper gastro-intestinal tract may be due to reflex stimulation through the intact left vagus nerve as well as to the poor condition of the experimental animal.

The introduction into the colon of Bagen's diplococci was not followed by a chronic colitis. We do not attach too much significance to this negative result however, because we do not know whether the organism used was pathogenic for dogs, and because we feel that the experiment was of too short duration.

SUMMARY

In dogs constant injection of small amounts of acetylcholine is followed by a hemorrhagic condition of the upper part of the gastro-intestinal tract, i.e., stomach, duodenum and jejunum.

Constant injection of medium amounts of pitressin is followed by hemorrhagic condition of the entire gastro-intestinal tract, especially of the lower ileum and colon. Attempts to effect sufficient liberation of pressor hormone from the pituitary by central vagus stimulation as well as attempts to produce chronic bacterial colitis were unsuccessful.

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Experimental Pancreatic Fistula; A Simple and Satisfactory Method for Investigating the External Function of the Pancreas

By

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WIRSUNG (22), the anatomist of Padua, in 1645 discovered the pancreatic duct and described the fluid which flows through it and DeGraaf (6) in 1664 made a pancreatic fistula with a wild duck quill as a cannula and collected one ounce of this fluid in about seven hours.

The first comprehensive studies of this sort, were made by Claude Bernard (2) in 1849, who inserted a silver cannula (Fig. 1) in the major pancreatic duct but he was unable to obtain a secretion lasting more than a few days. Bernstein (3) (1869) using lead wires was likewise unsuccessful. Pavlov (16) (1910) transplanted the pancreatic duct with a circular piece of duodenal mucosa (Fig. 1) surrounding the orifice into the anterior abdominal wall. He was the first to establish a successful fistula but the resulting proteolysis of the wound margins rendered this method impractical for prolonged investigation. Heidenhain (12) (1875) excised a cylindrical portion of duodenum (Fig. 1) including the duct papilla and transplanted it as did Pavlov. This led to a digestion of the abdominal wall as before. Finally Chepwallenkoff (4) (1899), one of Pavlov's pupils showed that the inactive trypsinogen was activated by enterokinase, a secretion of the duodenal mucosa.

Babkin (1) (1914) excised the offending duodenal tissue about the aperture of the duct before transplanting it (Fig. 1) but the resultant scar tissue formation about the fistula later interfered with the collection of the secretion.

A very ingenious but impractical method was described by Tuckerman (21) (1883), who inserted a large metal cannula (Fig. 1) through anterior abdominal wall into the duodenum in such a manner that the opening in the cannula was placed directly over the orifice of the greater pancreatic duct. The juice supposedly could then be obtained at any time by introducing a small catheter through the cannula into the duct.

The technic of Pavlov, with modifications, has been used by many others since; Senn (19) in 1886, Frouin (9) in 1913 and Inlow (13) in 1921. Senn was able to collect as much as 120 cc. per day (Fig. 1) but found that the amount secreted, quickly diminished and finally ceased, whereas, Inlow brought the duodenum up subcutaneously and anchored it to the rectus fascia. The pancreatic duct was then divided and led through a small stab wound to the side of the abdominal incision where it was sutured to the skin (Fig. 1). He kept his animals on soda bicarbonate and permitted them to lick their wounds during the intervals of collection. Consequently he observed no untoward results. Inlow also suggested a two stage operation as advantageous. In our hands, Inlow's method has not

been entirely successful. We found it troublesome to transplant the duct to the skin and get it to heal without retraction and subsequent cicatrization.

Other types of fistula have been described. Fodera (10) (1896) placed a T tube into the pancreatic duct so that the juice might go either to the duodenum or to the outside. It was similar in principle to a type biliary fistula described by Schiff (18) (1870).

In 1923, Rous and McMaster (17), while searching for a suitable method of permanent drainage of the common bile duct, discovered that rubber tubes could be maintained in the peritoneal cavity over considerable periods of time provided they were long enough and a strict asepsis was maintained. This type of intubation was employed by Elman and McCaughan (8) in 1926 in their studies on the fatal effect of the complete loss of pancreatic juice (Fig. 1). In twelve of the dogs studied by these authors the flow of pancreatic juice continued uninterruptedly after operation. In the absence of obstruction or infection which were the factors causing the greatest technical difficulty the secretion continued to flow profusely and the animals after a short time (five to eight days) died with symptoms of asthenia, vomiting, dehydration, and anorexia. Thus to quote Markowitz—"In the light these experiments (referring to earlier experiments where the fistulas were either subtotal or where the animals were permitted to lick the secretion), it seemed to be established that the loss of pancreatic juice to the outside was of little harm. Such a conclusion is erroneous. Elman and McCaughan made the classical observation that total drainage of pancreatic juice to the exterior resulted in the death of the dog in seven to eight days."

Gamble and McIver (11) (1928) used both kinds of fistula in their work on the acid-base composition of pancreatic juice, the pavlov type and the type described by Elman and McCaughan. Ivy and Farrell (14) (1926) made an autotransplant of the pancreas by dividing the body of the gland just distal to the large duct. This portion of pancreas was then brought up subcutaneously into the substance at the mammary gland (Fig. 1). The blood supply was left intact. Secretion occurred in the normal direction and was considered exclusively hormonal in origin as all nervous contact had been severed. This type of preparation while admirable for certain limited studies, is unsatisfactory for general physiologic observations due to: 1. The secretion is subtotal. 2. The transplant atrophies by approximately 50 per cent. 3. Interference with the nerve supply.

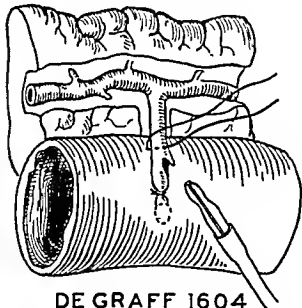
In an ingenious method described by Dragstedt et al (7), and based to some extent on the principle devised by Tuckerman, 1883, the common bile duct was implanted into the stomach and the first and second parts

*From the Department of Surgery, St. Louis University Medical School. Submitted March 31, 1939.

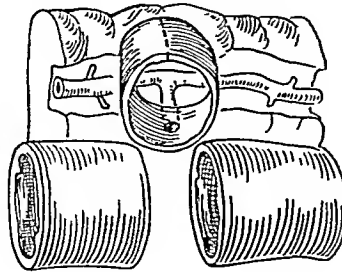
of the duodenum containing the terminations of both pancreatic ducts was prepared as an isolated segment. The continuity of the gastro-intestinal tract was restored by an end to side anastomosis between the stomach and third part of the divided duodenum. The isolated segment of duodenum was then cannulated

with a special gold plated cannula which was wrapped with omentum and then carried through a stab wound to the exterior where the secretions could be collected at intervals in sterile rubber bags (Fig. 1).

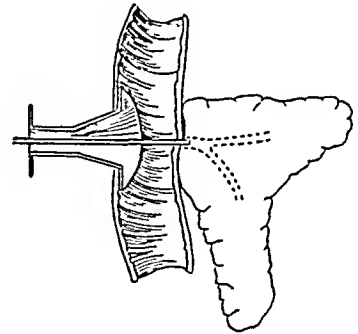
The objections to many of the methods just described have already been cited viz. Digestion of the



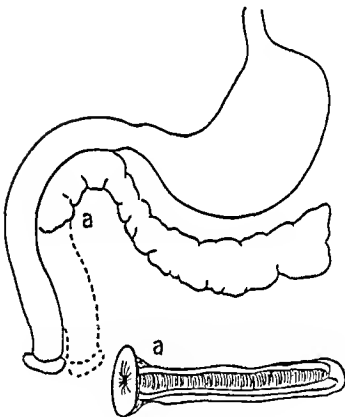
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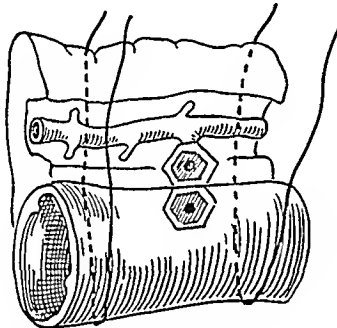
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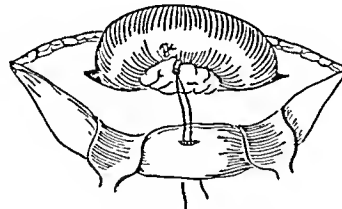
TUCKERMAN 1883



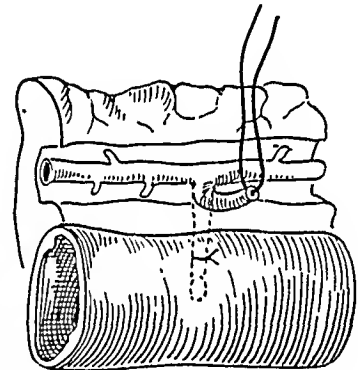
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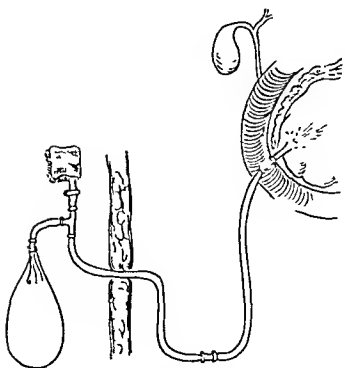
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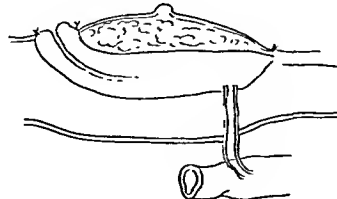
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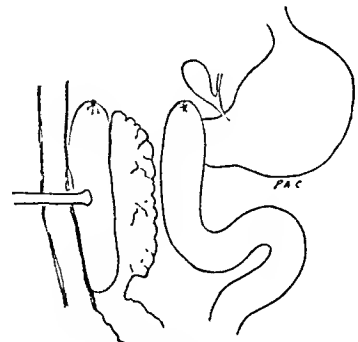
FROUIN 1913
BABKIN 1914
BOLDYREFF 1925



ELMAN AND MCCAUGHAN 1926



IVY 1925



ORAGSTED, MONTGOMERY, ELLER
AND MATHEWS 1930

Fig. 1. Sketches (diagrammatic) representing various types of external pancreatic fistulas used by different investigators.

adjacent abdominal wall, retraction of the duct, cicatrization about the fistula opening, premature discharge of the cannula and chronic ascending infections. To these should also be added the interference with the motility of the duodenum, the division of the nerve supply and the interference with the blood supply, dilatation of the pancreatic duct and atrophy of the acinar cells as a result of stenosis or partial obstruction. It seemed desirable if possible to design an external fistula which would as near as possible avoid these unphysiologic influences.

Coffey (5) in 1909, on the basis of some experimental work on internal pancreatic fistulae described an operation for resection of carcinoma of the head of the pancreas. The function of the remaining pancreatic tissue was to be preserved by inserting the resected stump into the intestine (Pancreato-Enterostomy). After transplanting the pancreas in this manner in dogs, Coffey noted that the pancreatic secretions emptied into the intestine irrespective of which end of the sectioned pancreas he implanted. In other

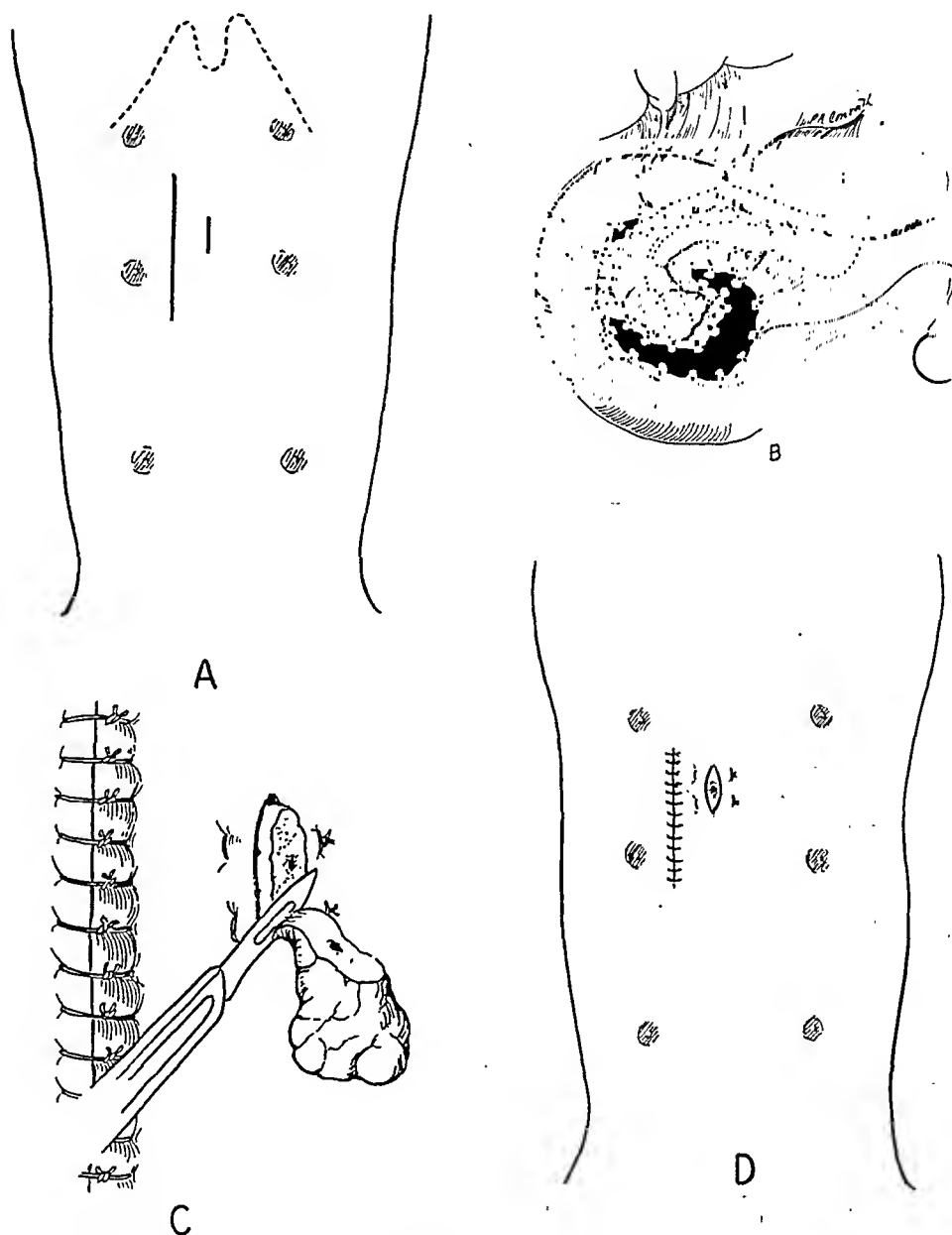


Fig. 2. Technic of the retrograde external pancreatic fistula. (a) Incisions. (b) The two pancreatic ducts are divided between ligatures and the distal segment or uncinete process of the gland is freed from its attachments. (c) The uncinete process is then drawn through the stab incision and anchored to the wound with mattress sutures avoiding constriction of the duct. The tip of the process is next amputated with a scalpel about one cm. above the level of the skin and the abdominal wound is closed in layers. (d) Final appearance of the fistula preparation.

words, the pancreatic juice could be made to flow normally or in a retrograde direction.

In 1934, Tripodi and Sherwin (20) conducted a similar series of experiments on dogs and showed that it was possible to implant the tail of the pancreas into the stomach and to obtain a retrograde flow of pancreatic juice, after ligation of the ducts of Santorini and Wirsung. Accordingly the principle of Coffey was applied to the formation of an external fistula described below.

EXPERIMENTAL METHOD

Under ether anesthesia and a strict asepsis, a right rectus incision is made (Fig. 2). The duodenum is brought up into the incision and the smaller pancreatic duct (Duct of Wirsung in the dog) is located and divided between ligatures. The larger duct or Duct of Santorini is then sought and dealt with in similar manner. Next the uncinate process is freed of its attachment to the duodenum and the duodenal mesentery and is brought up through a stab wound in the right flank.

The rent in the duodenal mesentery is carefully closed to prevent any possible herniation of intestine. The abdominal wound is next closed in layers and finally the tip of the uncinate process is amputated and the stump secured to the stab wound by through and through sutures without tension. No particular postoperative treatment is followed although the administration of soda bicarbonate to make up the alkali lost was recommended by Inlow. In a few days secretion commences and observations may be started. The stab wound heals firmly about the pancreatic stump. There is no interference with the motility of the duodenum or with its blood or nerve supply. The opening of the duct can be readily seen and cannulated using either a fine flexible silver cannula or a small segment of ureteral catheter, or the secretions may be counted directly or permitted to fall on a drop-recording apparatus.

PROTOCOLS

A female dog of 12 kgs. weight was operated on December 12, 1938, under ether anesthesia and a

pancreatic fistula produced according to the technic described above. The fistula secreted clear, odorless pancreatic juice intermittently and the animal was permitted to recover the secretions by licking the wound. Eight weeks later the animal was sacrificed and the pancreas removed for microscopic examination. Grossly there was no dilatation of the ducts and the sections showed normal pancreatic tissue.

A male dog of 14 kgs. weight was operated on December 15, 1938, and a retrograde fistula produced as previously described. This animal is living (March, 1939). The fistula secretes intermittently and the animal has been able to keep his weight and maintain his health. Increased secretion can be obtained by the injection of crude secretion or feeding at any time. A series of experiments on the secretion rate following the administration various substances are being carried out and will be reported later.

CONCLUSION

It is perhaps trite but a truism to say that advances in physiology depend to a considerable extent upon improvements in technical methods. Much of the data of classical physiology has of necessity been derived from acute mammalian experiments. The value of experimental data obtained from investigation of intact, unanesthetized animal preparations is self evident. In this respect study of external function of the pancreas is greatly favored by the use of total permanent external pancreatic fistula animals, in which unphysiologic factors are largely eliminated. The technic of fistula preparation described here (retrograde external pancreatic fistula) affords simplicity of technic with low immediate operative mortality and a high percentage of successful results. There is a minimum chance for pancreatic infection, and no interference with nerve supply and only a negligible interference with blood supply. No apparent atrophy of the pancreas was observed grossly or microscopically after four months.

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Editorials

THE CONTROVERSY OVER THE WOLDMAN PHENOLPHTHALEIN TEST FOR GASTRO- INTESTINAL ULCERATION

IN the June, 1938, issue of the *Journal*, Woldman published his test based on the principle that free phenolphthalein is absorbed from the gastro-intestinal tract when there is ulceration or some break in the continuity of the mucosa more easily than through the intact structures, and eliminated in part as free phenolphthalein in the urine.

The technique consists in giving the fasting patient 10 cc. of a 1% alcoholic phenolphthalein solution (prepared by dissolving 1 gram of white phenolphthalein in 100 cc. of 95% alcohol) mixed with 20 cc. of water. The urine is taken at two and four hour intervals and promptly tested with 10% sodium hydroxide for free phenolphthalein.

Fantus and Dyniewicz did pioneer work in the metabolism of phenolphthalein and reported (*J.A.M.A.*, 108:439-443, Feb. 6, 1937) that free phenolphthalein was usually absent in the urine after a small dose of the drug in normal individuals, but that conjugated phenolphthalein was always present. The latter does not produce a color reaction with sodium hydroxide. They found further that free phenolphthalein was constantly present in the urine after doses of 240 mgms. with excretion of 1 to 2 mgms. per twenty-four hours. The percentage of total phenolphthalein eliminated of the quantity ingested varies from 1.41 to 19.7.

In the April, 1939, issue of the *Journal*, Steigmann and Dyniewicz published an article with the very unqualified statement in their title that urinary elimination of free phenolphthalein was no test for gastro-intestinal ulceration. They imply that the free phenolphthalein in the urine is largely a matter of concentration of conjugated phenolphthalein present. However, it should be pointed out from their own data and graphs that there is a wide difference in the threshold of excretion of free phenolphthalein between normal individuals and patients when the concentration of conjugated phenolphthalein ranges from 1 to 2 mg. %. In this zone the percentage of positives in normal individuals ranges from zero to approximately one, but in patients it rises rapidly to nearly 40%. It can hardly be stated that the free phenolphthalein excretion is a simple function of the concentration of conjugated phenolphthalein. Furthermore, the greatest number of specimens were in this range of 1 to 2 mg. % concentration. Only at 5 mg. % concentration of conjugated phenolphthalein, according to Steigmann and Dyniewicz, does free phenolphthalein occur regularly in the urine. This concentration is rather rare after the 1½ gr. dose and might be reduced by greater dilution of the urine by a larger water intake. However, Woldman in testing normal internes and nurses asked them to limit the fluid intake so as to concentrate the urine and still obtained almost uniformly negative results. Steigmann and Dyniewicz, studying only 14 normal individuals, reported 41% of positive tests.

This is much higher than others have been able to obtain.

The discrepancy may be explained in part by differences in technique. To regard a barely perceptible trace of color as a frank positive is comparable to regarding a barely perceptible trace of color in a benzidine test for blood as highly significant. When the phenolphthalein solution is applied over an ulcerated surface such as epithelioma of the mouth there is a very deep color in the urine.

In the May, 1939, issue of the *Journal*, Kremer, Shore and Wiesel published a very fair report on the test in 137 patients. They found it correct in 79% of cases without evidence of gastro-intestinal disease and correct in 72% of gastro-intestinal cases which had been subjected to special gastro-enterological study.

All observers recognized early that cardiovascular renal disease and blood dyscrasias gave a high percentage of positives. There is obviously greater permeability of the mucosa under these circumstances and frequently multiple erosions and even gross ulcerations. Portis and Jaffe (*J.A.M.A.*, 110:6-12, Jan. 1, 1938) investigated the incidence of peptic ulcer in 9,171 consecutive necropsies and concluded that: "When peptic ulcer is the incidental lesion, it is most often associated with cardiovascular disease." Hence, positive tests under these circumstances must be interpreted with the above facts in mind.

Jaundice is apparently an absolute contraindication to the test. The conjugation of phenolphthalein with sulphates, glycuronates or other substances is believed to occur in the liver. This function seems to be suspended in jaundice and free phenolphthalein regularly appears in the urine. However, there are large numbers of cases in which there is no question of circulatory or liver disease in which the test may have a real field of usefulness. When there is doubt in regard to a large defect in the X-ray shadow of the stomach as to whether it is an intragastric or extragastric lesion, the test may prove to be quite helpful since there is a very strongly positive test when a large ulcerating surface is present.

False negatives are definitely known to occur when the solution of phenolphthalein does not actually come in contact with the lesion in the stomach because of food retained or exudate adherent to the ulcerated surface. In one case of carcinoma of the stomach the negative test was changed to a strongly positive one by thorough lavage of the stomach.

On the basis of the facts to date it seems that the dogmatic statement that urinary excretion of free phenolphthalein is of no value in the diagnosis of gastro-intestinal ulceration is unwarranted at present. It is obvious that there is a rather narrow spread between the doses of phenolphthalein that give negative and positive tests regularly in the normal. It is approximately 1½ grains in the former and 4 grains in the latter. Hence, quantitative determinations of the free and conjugated phenolphthalein may be necessary to sharply distinguish between positive and negative findings. What is needed is a more accurate determi-

nation of the facts and further clinical trial. More specifically, it would seem desirable that Steigmann, Dyniewicz and Fantus, who have done so much scientific work in this field, provide us with further quantitative results. Possibly the total phenolphthalein may be a useful determination since the percentage of total phenolphthalein eliminated of the ingested varies under different conditions from about 1 to 20%.

V. C. Rowland, M.D., Cleveland, Ohio.

WE welcome the appearance of a little journal called "Drug and Therapeutic Survey," which is published monthly at 55 Vandam Street, New York. The subscription price is \$5.00 a year. This journal is being published by Dr. Morton S. Biskind, who for more than five years was a member of the Headquarters Staff of the Council on Pharmacy and Chemistry of the American Medical Association. The idea is to supply to physicians unbiased critical information on drugs, therapeutic methods, and related topics. An effort will be made to provide data on important new drugs as quickly as possible after these drugs appear on the market. The little journal is attractive and is full of helpful and detailed information. It will tell physicians where they can get new drugs, how they are dispensed and what their value is likely to be.

Walter C. Alvarez.

HAS STRYCHNINE ANY VALUE AS A MEDICINE?

FOR years it has been the custom of many physicians to use strychnine as a nerve and heart tonic, and the drug is commonly added to laxatives, probably with the idea of toning up the activity of the colon. Actually, is there any real evidence available to show that strychnine is a tonic to nerves and heart and intestine? How does it really act?

We were so impressed recently with an article on the action of strychnine published by Heinbecker and Bartley in the American Journal of Physiology (125: 172) that we wrote Dr. Heinbecker asking him to give us his impressions of the possible value of the drug in medicine. As he and Bartley pointed out, many studies have shown that in the usually used small doses, the drug acts primarily on the central parts of the nervous system; it acts largely on the centers in the spinal cord and also in the medulla. As is well known, its principal action is to intensify reflexes largely by lowering thresholds for them. In large doses the intensity and duration of the reflex effect is increased until convulsions occur. These follow upon any type of sensory stimulation, and some convulsions seem to start even by themselves. Strychnine appears to act on both the sensory and motor parts of the reflex arc. Dusser de Barenne showed also that if strychnine is applied to sensory areas of the brain it gives rise to localized paresthesias. Several investigators have shown that even convulsive doses have little effect on the heart, the intestine, or the peripheral nerve ganglions. Alvarez was unable to show any effect of even fatal doses of strychnine on conduction in the bowel. Large doses may increase vasomotor tone, and larger doses injure the visceral ganglions.

During the last year Heinbecker and his associates at St. Louis have been using the cathode ray oscillo-

graph for a detailed study of the way in which strychnine acts on the axon, the synapse, on visceral ganglion cells, and on the spinal cord and brain. In dilute concentrations the effect of the drug on the axon is to lower its threshold, and in higher concentrations to raise it. The period during which two brief shocks will add up to produce a stronger effect is prolonged. With large doses the fatigability of the fiber is increased. In dilute concentrations the effect on synapses in the cervical sympathetic ganglion was a lowering of the threshold slightly if at all. In higher concentrations this threshold was raised and the absolutely refractory period was prolonged. Larger doses produced fatigue.

The effect on the spinal cord of the turtle, separated from the brain, was first to lower the threshold for reflex discharges, and in stronger concentrations to raise it. The irritability could be augmented to such an extent that a single shock applied to an efferent nerve trunk was followed by a continuous discharge of several minutes' duration. The effect on the cerebral cortex as measured by the response to stimulation of the saphenous nerve was a marked lowering of threshold for a first cortical response. Fatigability increased progressively.

Heinbecker and Bartley concluded that strychnine acts primarily on those neurons of the central nervous system whose discharge is associated with repetitive axonal responses. In lower concentrations it lowers the threshold of such cells and it facilitates their excitation. In higher concentrations it raises the threshold. While the action of strychnine is widespread in the nervous system, its effects are of consequence only in the brain and spinal cord because there one finds those cells which tend to discharge repeatedly and so to produce convulsions.

As Dr. Heinbecker writes, "From the standpoint of the clinician the recent studies would indicate that strychnine in therapeutic doses can be expected to increase the functional activity (tone) of the central nervous system and thus indirectly improve muscle tone, provided actual anatomical lesions of the nervous system do not preclude the possibility. In such doses no appreciable direct effect on the peripheral somatic or autonomic nervous systems could be expected. Strychnine is not an effective heart tonic nor a stimulant of gastro-intestinal activity. In large doses, through its action on the central nervous system, vasomotor tone is increased."

It would seem, then, that it is a waste of money to add the drug to laxatives, and it is a waste of time to give it to patients with heart disease. Because of its tendency to increase reflexes and to increase fatigability of parts of the nervous system, it would seem to be the worst possible drug to give to patients who are already tremendously on edge and jittery with exaggerated reflexes.

Walter C. Alvarez.

THE CHANGES IN THE GASTRIC MUCOSA SEEN IN CASES OF PERNICIOUS ANEMIA

ALTHOUGH it has for years been known that a primary macrocytic anemia is commonly associated with atrophy of the mucosa of the stomach, exact descriptions of the changes must still excite the interest of every internist. In the February, 1939, number of the American Journal of Medical Sciences,

Meulengracht of Denmark reported an interesting histologic study of nine stomachs and duodenums obtained from patients who died of pernicious anemia. The essentially new feature of the study was that the usual postmortal auto-digestion of the gastric mucosa was obviated by the injection immediately after death of 600 cc. of 5 per cent formaldehyde solution around and into the stomach and duodenum.

As was expected, in all cases Meulengracht found some atrophy of the mucosa of the fundus and body of the stomach. There was a little increase of round cell infiltration, but this was not pronounced. The crypts were usually shorter than normal, and they were more widely separated from one another by interstitial tissue. In some cases the crypts largely disappeared, and in others there were "islands" of intestinal epithelium. In some places there was a cystic dilatation of the lumens of the glands. Sometimes the mucosa was thin and smooth and almost without glandular elements. It should be noted however, that the appearance of the mucous membrane depended greatly on the extent to which the stomach was distended. Naturally if it was markedly distended, there was a greater appearance of atrophy and flattening of the mucosa.

Very interestingly, little atrophy was found in the mucosa of the pars pylorica. As Meulengracht says, he rather expected to find a special atrophy of the pyloric glands because he felt so sure that the anti-anemic factor of the stomach is produced in these glands. It was hard to say if there was any atrophy in the duodenum, and there didn't seem to be any change in the glands of Brunner.

Walter C. Alvarez.

A VALUABLE EARLY AMERICAN ARTICLE ON GASTRIC ANALYSIS

WE just ran on to a remarkable article by D. M. Cowie and J. F. Munson published in Volume 1 of the Archives of Internal Medicine. This article, written in the year 1908, deserves to be rescued from oblivion, and it should be known to all gastro-enterologists as a classic. It is remarkable for at least three things: In the first place, one finds here curves showing the results of fractional gastric analysis published some four or five years before the method became popular in the United States. In the second place one finds records of daily gastric analyses made on juice taken from one patient for a period of a month or two. Such studies have rarely been made. Finally, this article reports one of the earliest careful studies on the depressant effect of fat on gastric secretion. Dr. Cowie writes that he began this work in 1900 and reported on it in 1903.

Walter C. Alvarez.

INDIVIDUAL INSENSITIVENESS TO PAIN

ONE of many useful things that Emanuel Libman did for the medical profession was to point out that the syndrome of a disease can vary markedly simply because individuals differ greatly in their sensitiveness to pain. Thus the comparative insensitiveness to pain of many old people often enables cancer of some internal organ to grow to great size before the patient feels anything except perhaps some fatigue and weakness. Often the picture of peptic

ulcer is altered by the fact that the patient does not notice pain. We will never forget the big, husky man who came in with only one complaint, namely, that occasionally he had spells of violent retching. Aside from these spells he was perfectly well. Roentgenologic examination, and later an operation, showed a big duodenal ulcer perforating posteriorly. Ordinarily this would have given rise to attacks of excruciating pain, and the question arose: Why didn't it cause pain in this man? The answer was that this man didn't know what pain was; he went to sleep in the dentist's chair and once he had several teeth extracted at a sitting without any anesthetic and without any discomfort.

On the opposite side of the scale of sensitivity one finds, of course, women who feel so much and complain so much that a large part of their story of pain and soreness must be discounted. The physician can be fairly certain that much of what they describe as excruciating pain would be a discomfort to the average person.

It is interesting to note now in a report by Ford and Wilkins in the Bulletin of the Johns Hopkins Hospital for April, 1938, that insensitiveness to pain can be found in children. They report three such cases. Interestingly, these children did not show any real analgesia or any loss of sensibility, but they seemed merely to be indifferent to pain.

Many years ago on the Barbary coast in San Francisco, there was a town character who had discovered that he could make money out of his insensitiveness to pain. He would allow anyone coming into a saloon to knock him down if only they would then buy him a few drinks.

Walter C. Alvarez.

THE NERVOUS REGULATION OF FAT METABOLISM

AS anyone might have expected from observing that nervous persons are often thin in spite of a high caloric intake, it can be shown that the two functions of deposition and mobilization of fat in the body are influenced by the nervous system. The subject is touched on briefly in the 1938 *Annual Review of Biochemistry*. There Verzar pointed out that Beznák cut the splanchnic nerves on one side in a cat, and when the animal was starved, three times as much of the perirenal fat disappeared on the intact side as on the denervated side. When fat stained with sudan was fed, the concentration of the dye on the denervated side was seen to be about a fourth that on the normal side.

Unilateral extirpation of the cervical sympathetic ganglions had a similar effect on the amount of pericardial fat, and extirpation of the lumbar and sacral ganglions affected the deposition of the abdominal and subcutaneous fat. Similar observations were made by Hausberger. Kuré, Oi and Okinaka studied the distribution of subcutaneous fat after cutting anterior and posterior spinal nerve roots and found that fat deposition was increased when the anterior roots were cut, together with the sympathetic rami. Cutting posterior roots lead to a decrease in fat deposition. They thought that sympathetic nerves tended to mobilize fat. Further studies along this line should be made. Light might perhaps be thrown on the fact that in emaciated persons one sometimes finds the fat in the

breasts, in lipomas, and in the eye sockets largely untouched.

Wertheimer in a series of papers in Pflüger's Archiv., (213, 1926) reported curious observations on the fat deposition in dogs after the severing of the spinal cord about the level of the seventh dorsal vertebra.

One must wonder sometimes if the striking increase in weight which appears in some women immediately after marriage and in the absence of pregnancy may not be due partly to psychic or nervous changes as well as to changes in function of the ovaries due to the stimulus of intercourse. Another place in which nerves appear to have something to do with fat deposition is in cases of lipodystrophy. Sometimes a woman will be skin and bones from the waist up and plump from the waist down, and rarely one can see a woman who is emaciated on one side of the median line and well nourished on the other. Perhaps of interest in this same connection is the loss of fat in the thighs which comes in certain diabetics due to the frequent injection of insulin. Tremendous increases in body fat are seen also at times with lesions of the thalamic region.

Walter C. Alvarez.

A NEW JOURNAL OF GASTRO-ENTEROLOGY

IT is a pleasure to welcome the appearance of a new journal on digestive and metabolic diseases, the *Deutsche Zeitschrift für Verdauungs- und Stoffwechselkrankheiten*, edited by Max Bürger and Werner Catel and published by Johann Ambrosius Barth of Leipzig. The first number appeared in September, 1938, and already there have been published four numbers. The journal is attractively printed on excellent paper, on which the illustrations show up beautifully.

Several interesting papers have appeared. In the first number there were good papers on pancreatic stones, digestion in the small bowel of man, the roentgenologic diagnosis of carcinoma of the pancreas, non-tropical sprue, the Takata reaction, and the galactose tolerance of infants. In the second number there were articles on venous varices in the esophagus, the digestibility of uncooked starch, and a very interesting histologic study of the appearance of the gastrointestinal mucosa after the giving of tellurium salts. In number 3 there were studies on the estimation of ferments in the duodenal contents and on the frequency with which ulcer appeared in Munich during two different ten-year periods. Number 4 has an interesting and well illustrated paper on the appearance of the liver and spleen in roentgenographs after intravenous injections of Jodsolen. There is a pharmacological study of Prostigmin and its influence on the small bowel, and a study on absorption of Vitamin B₁ from the bowel. Each number contains several good reviews of articles and books. Many American gastroenterologists will doubtless want to subscribe to this excellent journal.

Walter C. Alvarez.

ALCOHOLIC GASTRITIS

IN view of today's upward surge of interest in gastritis, all gastro-enterologists will be interested in a paper by Seymour, Spies and Payne in the Journal of Clinical Investigation for January, 1939. They re-

port a study of 40 cases of chronic and long-continued addiction to alcohol. They used histamine as a stimulant to secretion. Contrary to what one would expect from today's teachings, in these cases there was no clinical evidence of vitamin deficiency and there were no signs of anemia. On the average, the secretory volume and the acidity were decreased, but the peptic activity of the gastric juice was apparently unchanged. There was a greater than normal incidence of achlorhydria. At times histamine failed to produce acid when at other times in the same patient it did produce an acid secretion.

Walter C. Alvarez, Rochester, Minn.

ANNOUNCEMENT

THE 18th annual scientific and clinical session of the American Congress of Physical Therapy will be held September 5, 6, 7, 8, 1939, at the Hotel Pennsylvania, New York City. Preceding these sessions the Congress will conduct an intensive instruction seminar in physical therapy for physicians and technicians—August 30, 31, September 1 and 2.

Physicians are urged to plan their vacation for these periods and bring their families to New York for the World's Fair. Ample time has been provided for during the convention to visit the fair and to enjoy the various activities of America's metropolis.

While the convention proper will have numerous special program features of scientific interest, the added attraction of the World's Fair should make it extremely worth while for every physician to come to New York and spend a most profitable vacation.

The instruction seminar should prove of unusual interest to physicians and technicians. The clinics which comprise half of the schedule make this course outstanding for its practical value. As in the past outstanding clinicians and teachers will participate. Registration is limited to 100 and is by application only. For information concerning seminar and preliminary program of convention proper, address American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

ANNOUNCEMENT

THE University of Wisconsin Medical School is to conduct an Institute for the Consideration of the Blood and Blood-Forming Organs, September 4-6, 1939. The program is to include papers and round-table discussions by European and American workers in the field of hematology. In addition to the discussions, the following formal papers are to be presented:

Dr. L. J. Witts, Oxford, England, Anemias Due to Iron Deficiency.

Dr. Cecil J. Watson, Minneapolis, The Porphyrins and Diseases of the Blood.

Dr. Cornelius P. Rhoads, New York, Aplastic Anemia.

Dr. E. Meulengracht, Copenhagen, Denmark, Some Etiological Factors in Pernicious Anemia and Related Macrocytic Anemias.

Dr. Harry Eagle, Baltimore, The Coagulation of Blood.

Dr. George R. Minot, Boston, Anemias of Nutritional Deficiency.

Dr. Russell L. Haden, Cleveland, The Nature of the Hemolytic Anemias.

Dr. Jacob Furth, New York, Experimental Leukemia.

Dr. Claude E. Forkner, New York, Monocytic Leukemia and Aleukocytic Leukemia.

Dr. Edward B. Krumbhaar, Philadelphia, Hodgkin's Disease.

Dr. Louis K. Diamond, Boston, The Erythroblastic Anemias.

Dr. Edwin E. Osgood, Portland, Marrow Cultures.

Dr. Charles A. Doan, Columbus, The Reticulo-Endothelial System.

Prof. Hal Downey, Minneapolis, Infectious Mononucleosis.

Dr. Paul Reznikoff, New York, Polycythemia.

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Dr. Ovid O. Meyer, Chairman of Program Committee, University of Wisconsin Medical School, Madison, Wisconsin.

ANNOUNCEMENT

THE ninth annual Convention of the Biological Photographic Association will be held September 14-16th, at the Mellon Institute for Industrial Research, Pittsburgh, Pa. The program will be of interest to scientific photographers, scientists who use photography as an aid in their work, teachers in the biological fields, technical experts and serious amateurs. It will include discussions of motion picture

and still photography, photomicrography, color and monochrome films, processing, etc., all in the field of scientific illustrating. Up-to-date equipment will be shown in the technical exhibit; and the Print Salon will display the work of many of the leading biological photographers here and abroad.

The Biological Photographic Association was founded nine years ago because of the growing need for expert illustrative material for scientific research and teaching. Many workers were solving their problems in their own way. But obviously they were wasting time and effort in individually repeating experiments that had been worked out elsewhere. The B.P.A. was formed to act as a clearing house for new ideas, to pool experiences, record standard procedures and disseminate information. Its aims were scientific and all services have been volunteered by officers and members on a non-profit basis.

The B.P.A. Journal is published quarterly, constituting a Volume of about 250 pages, which is furnished free to members. Membership privileges include an authoritative question and answer service; also the right to borrow loan albums and exhibits of scientific prints for study and display.

Further information about the Association and the Convention may be obtained by writing the Secretary of the Biological Photographic Association, University Office, Magee Hospital, Pittsburgh, Pennsylvania.

Book Reviews

"*The Restoration of the Peasantries.*" By G. T. Wrench, M.D. (Lond.), C. W. Daniel Co., Ltd., 40 Great Russell St., London, W.C.1. (\$1.60).

G. T. WRENCH, a doctor of medicine, has become interested in the subject of soil fertility, because it has an eventual bearing upon the subject of human disease, as he so graphically proved, or seemed to prove, in a previous book, "*The Wheel of Health*," which was reviewed in this column. Briefly he showed that unless a soil is carefully fertilized by means of special composts, representing decayed natural products, as distinguished from artificial fertilizers, it fails to produce foods containing those substances, known and unknown, which combine to offer perfect health to a populace. We understand that Wrench's work has received considerable recognition by the British Government in recent months. His claims as stated in the previous work were so striking, that, although logically supported by evidence of a scientific character, they seemed to carry with them a possible exaggeration. Thus it did not seem possible that the perfect health of the Hunzas could be dependent wholly upon the fact of their outstanding proficiency as an agricultural people. But Wrench's work was well controlled and, to the reviewer at least, it was convincing. In that important book he indicated that perfect health was within the grasp of any people who consistently generation after generation, utilized the special natural composts, and ate an abundance of fresh vegetables, fruit, dairy products and a minimal amount of meat. It appeared that such food *only* if grown in accordance with the principle of returning

to the earth its natural foods, would confer upon a populace a state of health which was almost, if not quite free from disease.

In a new book, "*The Restoration of the Peasantries*," Wrench again holds up the important principle of true soil fertility, and shows at some length that today most if not all nations are suffering from a recession of soil fertility. This has been caused essentially by a failure in the true individual care of land tracts, especially a lack of natural fertilizing composts. That this is the case cannot be doubted in the least, and the continued insult to the soil of taking from it year by year without making a proper return, is the basic explanation of the disappearance of the humus, with resultant erosions and ultimate unproductivity. Already, the results are seen in vast areas of aridity everywhere including notably sections of the United States.

Under the ancient peasantries in India, China and elsewhere, a small farm of say 4 or 5 acres was the sole wealth of a peasant family, and it was tilled with an attention to every detail, as a very personal matter, especially with respect to constant proper fertilization with natural phosphatic and nitrogenous composts. In China, for example, under this ancient system which only within the last century has given way to more modern methods, a living and constant productive soil was maintained for at least 30 centuries. The advent of capitalistic farming, wherein land represents mortgagable property, and where, because of the nature of capitalism, the chief object was to get out

of the soil as much as it could give without proper return ever being made, has seen the rather rapid deterioration of the soil fertility. Along with this has come an unfortunate enslavement of the farmer himself, so that eventually, because of falling fertility, he plays irrevocably into the hands of the land owner and eventually into the hands of the banker.

Possibly one way to achieve a return to sane farming for the purpose of growing truly healthful food would be a return to the peasantry itself. In some parts of the world this seems possible. It must strike us as being utterly impossible in others, however. Indeed, history is not full of a "return" to anything. The world makes itself into a linear moving diagram for better or for worse, but, apart from the reestablishment of the peasantries, we must not overlook the broad yet specific moral in Wrench's careful work. It is simply this—whether or not capitalistic farming has come to stay, we must not expect to obtain really healthful foods from a system which neglects proper soil fertilization, for it cannot be so obtained. This book continues to strengthen the lesson of his last one. It has so profound a bearing upon individual and national health, and is so dramatic in its lucid presentation, that it must be considered a work of urgent and primary importance in the broad field of hygiene and preventive medicine.

Good Morning, Doctor! By W. A. Rohlf, Cedar Rapids, Iowa. The Torch Press, 169 pp., 1938.

ANYONE who has had the pleasure of knowing Dr. Rohlf will be particularly pleased with this delightful little volume. It describes in a series of brief chapters the struggle of a poor boy to get an education, and then his development until he came to be one of the ablest and most respected and most loved surgeon of Iowa. The book tells of many interesting trips made out through blizzards and at night in sub-zero weather. It tells of operations on the kitchen table, and of the many brave deeds that a horse and buggy type of doctor has always done. There are many pages in the book which will give the reader thrills up and down his spine, and some will bring the mist to his eyes. This would be a splendid little book to place in the hands of a medical student or a young physician starting out in general practice. There are few books that could give him a greater feeling of respect for the profession he is entering. Few could excite in him such feelings of consecration. This book will doubtless bring to Dr. Rohlf many more friends to add to the thousands he already has.

You Can't Eat That. By Helen Morgan. Harcourt, Brace and Company, New York, 330 pp., 1939. Price \$2.50.

ONE of the great problems of the highly food-sensitive person is to find new foods to take the place of those that he has had to give up. Another great problem is to devise dishes and breadstuffs which, while tasty enough, will not contain offending substances. Many a mother who has had to struggle with the problems of catering to asthmatic, eczematous or hay-feverish children will doubtless welcome this book by Miss Morgan, with its many

recipes for dishes suitable for persons suffering with food-sensitiveness.

One of the most helpful parts of the book may prove to be Part 3, entitled "What's in it?" Here the person who is highly sensitive to one or more foods can find out where his *bête noirs* are likely to appear and what sauces or dressings or bottled or canned concoctions he must leave alone. For instance, the man who is highly sensitive to egg will find that root beer contains egg white to make it foam and some wines have had egg white added to clarify them. The book should be added to the library of every allergist.

The Theory and Practice of Personal Counseling. By Hugh M. Bell, Stanford University Press, 167 pp., 1939. Price \$1.25.

IT would be a tremendous help to internists and perhaps particularly to gastro-enterologists if there were some method by which a quick and fairly accurate estimate could be made of the patient's temperament and psychological makeup—an estimate which would help the physician to recognize the presence of a neurosis and the probable causes for it. With these facts in hand fewer persons might be operated on fruitlessly.

Obviously, of course, every physician of experience will size up a patient as he or she goes through the office. He will note the way in which the history is told and the way in which the patient behaves during the interviews and during the examinations. But even when, after thirty years of practice, he has become expert at sizing people up, he may still, from time to time, be so completely deceived that he will be tremendously surprised when he learns that the beautiful and very pleasant woman whom he enjoyed meeting in the office has been in an insane asylum more than once, and is a devil at home.

This little paper-bound volume by Professor Bell will introduce physicians to a literature and a technic which will be entirely unknown to many. It was designed particularly for the helping of student counselors who want to find quickly which of their pupils are poorly adjusted and which are likely to have trouble with their studies and with their comrades. Each student is given a list of 140 questions which he must answer with yes or no. Each answer is weighted with a number + or —, and if the algebraic sum of these weights is above a certain figure, the psychologist can be pretty sure that there is some maladjustment to life, and going over the answers he can get a quick insight into what the principal difficulty is.

The probability is that within another twenty years questionnaires of this type will be filled out routinely by all clinic patients and perhaps by many patients consulting up-to-date internists.

The Newer Knowledge of Nutrition. By E. V. McCollum, Orient-Keiles, Elsa and Day, H. G., New York. The Macmillan Company, 701 pp., 1939. Price \$4.50.

THIS fifth edition of a standard text is most welcome. The fourth edition has been out of print since 1935. The present text represents a complete re-writing. The book represents our ideal of a book which, while concentrated and shortened so far as is possible, contains all the essential information that is needed even by the expert and the specialist. So often

the author who tries to simplify his subject and to produce a small book ends up with one that is too sketchy to be of much use to anyone except perhaps a high school student.

Dr. McCollum and his two associates have attempted "to prepare a concise survey of the field of nutrition which is more extensive and more inclusive than any other now available, and which is kept close to the scientific literature by means of citations from carefully selected references for the benefit of those who may care to extend their reading in the original literature. It is hoped that the book will meet the needs of all who are, like the authors, seeking to determine what is sound and what is speculation or misinformation in respect to the nutritive needs of several species, including man; the dietary properties of food-stuffs; the characterization of malnutrition due to specific or multiple deficiency states; the occurrence of various types of malnutrition in man and animals in different parts of the world; and the means of dealing effectively with these nutritional problems."

The text is easy to read, and every chapter contains a valuable bibliography. We rejoice to see Chapter 26, which describes briefly the dietary habits of many primitive peoples throughout the world. It has always seemed to us that one of the defects in modern dietetics has been its tendency to base all teaching on what happens to a white rat when it is placed on a restricted diet. Just as interesting and perhaps just as helpful clinically might be a study of what actually happens to human beings in various parts of the world as they try to live on peculiar and narrow diets.

We heartily welcome the new book and congratulate Dr. McCollum and his associates on the completion of a splendid piece of work.

Sulfanilamide Therapy of Bacterial Infections. By R. R. Mellon, Paul Gross and F. B. Cooper, Springfield, Charles C. Thomas, 398 pp., 1938.

THIS is an excellent and most timely book. Section 1 deals with the chemistry of sulfonamide and related compounds, the pharmacology of these compounds, and experiments in vitro and in vivo which showed the way in which these drugs act. Section 2 deals with the authors' experiments with the bacteriostatic effects of sulfanilamide in vitro and the results in therapy with sulfonamide compounds on streptococcal and pneumococcal infections in laboratory animals. Section 3 deals with the mechanism of action of sulfonamide compounds and the mobilization of the defensive factors of the host. In an appendix there is a discussion of the photosensitizing and allergic-like actions of sulfanilamide, also details in regard to the production by the drug of sulphemoglobinemia.

There are other short sections on the effect of sulfonamide compounds on staphylococcal infections and on the filterable viruses, also one on the marrow culture medium for bacteriostasis tests in chemotherapeutic studies. One of the most hopeful things about the sulfonamide compounds is that some of them appear to be effective in combating a few of the diseases due to the filterable viruses. Unfortunately none of these compounds have yet shown any activity against the influenza virus or the St. Louis type of encephalitis virus. Some do protect against inoculation of the virus of choriomeningitis, and it is claimed that

certain of the drugs are effective in canine distemper. Sulfanilamide has been found helpful also in cases of lymphogranuloma inguinale, and it is proving very helpful in clearing up trachoma in the American Indians.

There is a bibliography of 300 titles which will be very helpful to all students of this important subject. This is a book which should be in every clinic in which these new drugs are being used.

It is a curious story the way in which prontosil and sulfanilamide were discovered. Some work was done by Domagk in the dye works in Germany, and in succeeding years some research was done on these drugs and related dyes which suggested that they might be valuable in medicine. Only gradually did it become apparent that they could have great value.

Textbook of Experimental Surgery. By J. Markowitz, Baltimore, Wm. Wood & Co., 527 pp., 1937. Price \$7.00.

WE are enthusiastic about this book. There was a need for it and Markowitz has done an excellent job. As he says, no one can become a surgeon by watching operations; he must get his hands in, and the place to do this first is not in the hospital; it is in the laboratory of experimental surgery. The best surgeon, also, is likely to develop out of a gifted young man who spends much time in the physiologic laboratory doing experiments which involve difficult surgical technic and which throw light on some of the problems still bothering the medical profession. One of the best places in the world for the doing of this type of work is the Institute of Experimental Medicine of the Mayo Foundation, presided over by Frank Mann. There Markowitz worked, as he says, for three happy years, and much of the material in this book is based on the researches of Mann and his staff and his many students.

The book is beautifully illustrated and well and interestingly written. Markowitz is a dynamic, interesting sort of a man with a gift for unorthodoxy. He believes rightly that every lesson should be made interesting. As he says, in the case of science, if the lesson is not interesting one can be fairly certain there is something wrong with the teacher.

The field covered by the book is large. One finds even a chapter on antivivisection. Actually, this is as it should be, because no director of a laboratory can afford to be ignorant of the wiles of those women who vent their spleen on physicians and attack modern medicine behind a mask of zoophily.

Every physiologist and every experimenter on animals will want to have a copy of this book, and for years to come it will doubtless be the Bible of every student of experimental surgery. Included in almost every chapter is much physiologic information, and at the end of each chapter is a valuable bibliography.

Zwanglose Abhandlungen auf dem Gebiete der Frauenheilkunde. Vol 1. Normale und pathologische Physiologie im Wasserhaushalt der Schwangeren. By Herbert Albers, Leipzig, Georg Thieme, 119 pp., 1939.

THIS is the report of extensive studies made on the water balance of the body during pregnancy and labor. There are studies of normally pregnant women and pregnant women with marked edema. It appears

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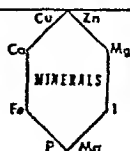
1. Allen, A. M.—*Medical Record*,
April, 19, 1939.

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that there is an increase in the amount of blood in pregnancy with a marked increase in the plasma. This produces an apparent diminution in the number of red corpuscles.

The monograph will be of much interest to obstetricians and to all students of blood volume and of the water content of the tissues.

Nutritional Physiology of the Adult Ruminant. By E. G. Ritzman and Francis Benedict, Washington, D. C., Carnegie Institution, 200 pp., 1938.

In this book the chapter on the physiology of digestion, absorption and elimination of waste products by

the ruminant will be of interest to gastro-enterologists, and particularly to those who are interested in flatulence and constipation. There are a number of tables with data showing the amount of methane produced by herbivorous animals on various diets. Due to the excretion of methane through the lungs or the esophagus a cow loses on the average 9.6 per cent of the digestible energy in the food. In one day an elephant can eliminate through lungs, esophagus and anus from 500 to 800 liters of methane.

It is an interesting fact that an elephant which consumes during the day 50 kilograms of hay, will pass

from 84 to 137 kilograms of feces. A horse which may eat during the day 10 kilograms of hay will void feces weighing 20 kilograms. Most of the added weight is due to water. The daily fecal excretion of a Jersey cow can be 7 per cent of her weight. Apparently with a herbivorous diet a tremendous amount of water must be taken in if only to keep the rough material flushing through the intestine. A carnivorous animal passes a much smaller amount of feces and is much more likely to become constipated.

Consultation Room. By Frederick Loomis. Alfred A. Knopf, New York, 281 pp., 1939. Price \$2.50.

Publishers have learned in recent years that every wide-awake man or woman with a little strain of curiosity in his or her makeup is eager to see how other people live and work and do the things they have to do. We all enjoy learning how a great hotel is run or what a captain of a great liner has to do each day; we probably would be intensely interested even in a well told story of the daily problems of the town dog catcher.

For years the medical profession frowned so severely on any of its members who dared write for the lay public that it was difficult for publishers to get biographical material out of those physicians and surgeons whose lives and experiences were most worth telling about. Able and successful men with vivid personalities were begged to write, but all but a very few were unwilling to do anything that might lessen the goodwill and esteem of the colleagues with whom they had worked throughout a lifetime.

Today this barrier of reserve and tradition is being broken down, and many physicians are coming to see that the medical profession is not only not hurt but is actually helped when some of its ablest members describe well and vividly the life that a fine physician leads: a life filled with tremendously hard work and motivated by feelings of consecration and devotion, not only to the man's science and art, but to the needs of humanity in general and of suffering individuals in particular.

Probably at no time in the history of this country could medical biographies of this type do more good than at present, when in Washington plans are being made to regiment a large part of the medical profession; to put physicians on salaries and to take away from them most of their incentive to advance themselves in knowledge and skill and in the good graces of their patients.

Faced with this menace, the medical profession might well have considered employing some type of public re-

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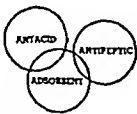
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lations counsel such as many big firms now call in when attacked by the government or the press, but then along came Dr. Hartzler with his vivid story of the "Horse and Buggy Doctor," a story which showed the public that physicians of the finest type have been giving generously and often without reward a service for which no one but a very wealthy man could pay. No one but a brave devoted public servant would be willing to start out at night through blizzard and storm and flood and to risk his life for a stranger.

Now comes Dr. Loomis with a book which is a worthy companion to Dr. Hertzler's, although it describes a

very different type of practice, one in which the consultant sits for half his day at his desk in a big city office building and during the rest of the day and part of the night works in the lying-in and the operating rooms of a great hospital. Although one cannot expect to find here tales of brave struggles against snow and high water and savage dogs one does find stirring pictures of courage and devotion and consecration, of resourcefulness in the daily fights against disaster and death, and of sympathetic efforts to save the self-respect of young women who, having loved too deeply and too generously, find themselves facing unmarried mother-

hood. One sees that the successful city consultant and surgeon must have a big heart; he must have courage and he must be a born leader, upon whose broad shoulders men and women find it easy to drop their burdens. Dr. Loomis shows the picture of a busy city consultant sometimes spending days worrying over the problem of some poor girl who can't possibly repay him for all the time he gives her. Actually, he gave this time and effort because he was as much concerned for the patient's soul and happiness as he was for the salvation of her body.

This is a splendid book, well written, and full, not only of soul stirring and thought producing stories, but of helpful information for women of every age. Every puzzled woman going through the menopause would do well to read the chapter on her problems. The fact that the book has already gone into several printings shows that it is receiving a warm welcome from the public. Many readers will thrill over the stories of the unmarried women and the babies that were saved to them.

Every physician should be grateful to Dr. Loomis for having written this book. As stated in the early part of this review, if the book had been written years ago it would have brought down on Dr. Loomis' head much criticism and perhaps some ostracism, but today most physicians can see how much good such a book can do, not only to laymen but to young physicians starting out on their career, and to the cause of scientific medicine everywhere. Perhaps through books like this the reading public will at last come to see how desirable it is that the medical profession be supported in its efforts to put down quackery both within and without its ranks. Actually, physicians who might still be inclined to deprecate such writing by their colleagues will doubtless note now that the best of these medical biographies are being written, not by young men who might perhaps be suspected of trying to build up prestige and a practice, but by men who are approaching the close of their professional life, and who for years have carried a much larger burden of practice than they wanted. They can hardly be accused of trying to drum up practice.

Die Viscerographische Methode. By D. Danicopolu, Berlin, S. Karger, 166 pp., 1930.

This book is of greater interest today since Osler Abbott has been showing what can be accomplished with an intestinal tube. Danicopolu and his collaborators were some of the pioneers in this field, and it is interesting to see what they accom-

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plished. They report many physiological and pharmacologic experiments not only on animals but on normal and diseased men. In these experiments from one to three recording balloons were passed into esophagus, stomach, small intestine, colon or bladder.

Danielopolu believed that this type of work should be of great value to the clinician but the reviewer could not find in the rather verbose discussion of the experiments much to support the statement. Danielopolu felt that his experiments were of great value also in showing how different the pharmacologic reactions

of the digestive tract are in man and in laboratory animals. Actually, the reviewer's impression from the many good copies of kymographic records which are here published is that drug actions are much the same in animals and man. The striking fact which the clinician might do well to grasp is that most of the drug-actions were fleeting. The physician, when he gives a drug has in mind and usually desires an action which will last several hours or all day; Danielopolu's records show that the action usually lasts seconds or minutes; that it is often a mixture of inhibition and stimulation, and that this mixture

varies with the dosage of the drug used.

The book really constitutes a valuable and unusual contribution to our knowledge of the motor functions of the digestive tract. There is much information of value about the behavior of esophagus, stomach and bowel. It is interesting to see that years ago Danielopolu found that atropin and eserine will sensitize the gastric musculature so that it will become more sensitive to psychic stimuli. Such observations have been repeated of late.

The esophagus in cases of cardio-spasm gave a peculiar record with the balloon technic. Large doses of ephedrin quieted the intestine for several minutes. Pilocarpin produced a temporary increase of gastric motility followed by a period of quiet. The effect of adrenalin was found to last but a few seconds. Small doses of atropin seemed to increase the activity of the stomach but large ones inhibited it. The book should be studied by everyone who is interested in the research side of gastro-enterology.

Zwanglose Abhandlungen auf dem Gebiete der Frauenheilkunde. Vol. 2. Der Aneurin- (Vitamin B₁) haushalt in der Schwangerschaft und im Wochenbett. By Gerhard Gaetgens, Leipzig, Georg Thieme, 76 pp., 1939. Price 6.70 RM (bound).

This small monograph contains results of careful studies of the excretion of Vitamin B₁ in the urine and feces of pregnant women. There are also studies of the amount of B₁ in the serum, the placenta and the milk. Lactation didn't appear to influence the level of Vitamin B₁ in the body. There didn't seem to be any greater need for the substance during pregnancy and lactation. It didn't seem to Dr. Gaetgens that the lack of B₁ could explain any of the pathologic manifestations seen in some pregnancies.

Abstracts

SCHATZKI, RICHARD.

The Roentgenologic Appearance of Intussuscepted Tumors of the Colon, with and Without Barium Examination. Am. J. Roent. and Radium Therapy, Vol. 41, No. 4, pp. 549-563, April, 1939.

The occurrence of intussusception of tumors of the colon is a rare enough occurrence to warrant the report of eleven instances seen at the Massachusetts General Hospital by Dr. Schatzki, during the past three and one-half years.

Of these eleven cases, the site of the tumor was the caecum in four instances; in three instances, hepatic

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RAHWAY, N. J.

flexure was involved; in two instances, the ascending colon. In one instance, the transverse colon, and in another case, the sigmoid. In seven cases, the tumor was an adenocarcinoma—in three cases, it was a submucous lipoma which all showed partial necrosis and ulceration, and in one case, the histology was unknown.

The roentgenologic signs of intussusception are analyzed, using as a model a figure showing three concentric cylinders; a narrow central canal surrounded by a thin peripheral sheath, which are separated by a

wide space representing the mesentery of the two intestinal walls, and finally the distal intestinal wall.

Examination of these cases may be done in one of three fashions:

I. Barium Enema:

(a) The enema may stop suddenly with the formation of a cap.

(b) The enema may enter the sheath surrounding the intussuscepted gut producing two peripheral lines of barium outlining the profile of the non-filled intussuscepted gut. On occasion, circular bands forming a spiral-like picture around this part of the gut may be seen.

(c) The enema may enter the lumen of the intussuscepted gut.

II. Peroral Examination:

In this case the central canal may be filled as well as the sheath. The caliber of the gut may change suddenly and may have the shape of a bird's beak.

III. Flat Film:

In instances of small bowel obstruction, air- and fluid-filled dilated loops are seen. However, in cases of large bowel obstruction there may be an absence of gas in the hepatic flexure and small loops of bowel may occupy that region. Likewise, the absence of the normal pattern of the air- and fecal-filled caecum and ascending colon is a common and valuable sign.

There are several other diagnostic aids which may be obtained from the flat film alone:

(1) The area of intussusception is characterized by a sausage-shaped homogeneous shadow.

(2) This may be surrounded by an air-filled sheath, or by air rings.

(3) The shadow of the intussuscepted gut is differentiated from that of the fecal mass by its homogeneity as compared with the mottled appearance of fecal material.

(4) The tumor causing the obstruction can sometimes be seen.

(5) At times, a narrow air-filled lumen surrounded by a thick soft tissue cylinder may be seen.

(6) The beak-like appearance of the gut entering the area of intussusception is characteristic.

(7) The portion of the colon proximal to the intussusception may appear unusually short. There may be gross obstruction with distended air-filled gut proximal to the intussusception.

The two important factors in the differential diagnosis are:

(1) Is an intussusception present?
(2) What type of intussusception is present?

Two diagnostic pitfalls are mentioned:

(1) The inverted caecum in intussusception may simulate a mass when no mass is present.

(2) The narrowed piece of intussuscepted gut may lead to a diagnosis of regional ileitis because it may simulate the "string sign" of ileitis.

A question as to what part of the gut is involved is important. In colonic intussusception enough of the proximal colon is visible to mark off the beginning of the process. It is, however, difficult to decide whether the intussusception at times arises from the ileum or from the caecum. In the former instance, the caecum is routinely inverted, whereas in the latter it is not always involved. They may also be differentiated by the fact that the continuity of the outline of



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the ascending colon is interrupted at the beginning of the intussusception of the colocolic type. It is not interrupted in the ileocolic type.

Although clinical symptomatology of intussusception is not discussed in this paper, one important symptom which occurred in eight of the eleven cases was named. This was the occurrence of repeated cramp-like pains in the abdomen of short duration, more or less severe and sometimes accompanied by fainting spells.

The article is accompanied by illustrations, both X-ray and diagrammatic, which are extremely interesting and lucid. It emphasizes the value of the study of soft tissue shadows seen on

the flat film in cases of intussusception.

Henry H. Lerner, Boston, Mass.

KIRSNER, JOSEPH B. AND MILLER, JOHN FRANCIS.

The Roentgen Diagnosis of Intussusception. Radiology, Vol. 31, 6, pp. 658-669, Dec., 1938.

The authors distinguish four common types of intussusception.

1. Ileocecal—the most frequent, in which the ileum and ileocecal valve pass into the cecum.
2. Colic—in which the large intestine is prolapsed into itself.
3. Enteric (ileal)—in which the small bowel alone is involved.

4. Ileocolic—in which the ileum prolapses through the ileocecal valve.

The best procedure is the examination by contrast enema. The careful study of the colon after filling and post-evacuation is necessary. As the enema is administered, a hindrance of the flow of barium usually occurs. This obstruction is produced by the apex of the intussusceptum and contraction of the ensheathing layer. If the invagination is loose, the obstruction will often recede for a varying distance by increasing the pressure of the enema. Under such circumstances there is an irregular filling of the colon proximally. Complete reduction may result, allowing the colon to fill out normally. This fact has encouraged the use of the barium enema for therapeutic as well as diagnostic purposes in selected cases.

However, movable obstruction is not completely diagnostic of intussusception since pedunculated tumors can give similar findings. If barium is able to pass between the sheath and the invaginated portion, a characteristic forking of the contrast substance occurs at the point of obstruction. The barium diverges into two narrow channels enclosing the intussusception as a thin cylindric shell within the intussuscepti. The length of the forking depends on the length of the invagination and on the anatomic space between the cylinders. It is possible, of course, that any rounded mass projecting into the lumen of the bowel, but completely obstructing it, will present a similar appearance. Further stress has to be laid on the presence of a palpable mass in the abdomen. The roentgenograms covering one colic and six ileocolic cases of intussusception illustrate these important points.

Franz J. Lust, New York, N. Y.

KANTOR, JOHN L.

The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions. "Practical Value of the 'Moulage Sign.'" Am. J. Roent. and Radium Therapy, pp. 758-778.

The disease syndrome which has been called "idiopathic steatorrhea" is characterized by an inability to absorb fat, carbohydrate, calcium, and sometimes phosphorus, along with anti-anemic factors and vitamins.

Clinically this condition is recognized by changes in the stool due to an increase of fatty content. There is very often a diarrhea of a frothy or soapy stool. Changes in the nervous system occur due to loss of calcium and result in irritability, tetany, and spasmodic. The skeleton may show osteoporosis and dwarfism. Opacities of the lens are often present. Anemia, tongue lesions, skin lesions, and dis-



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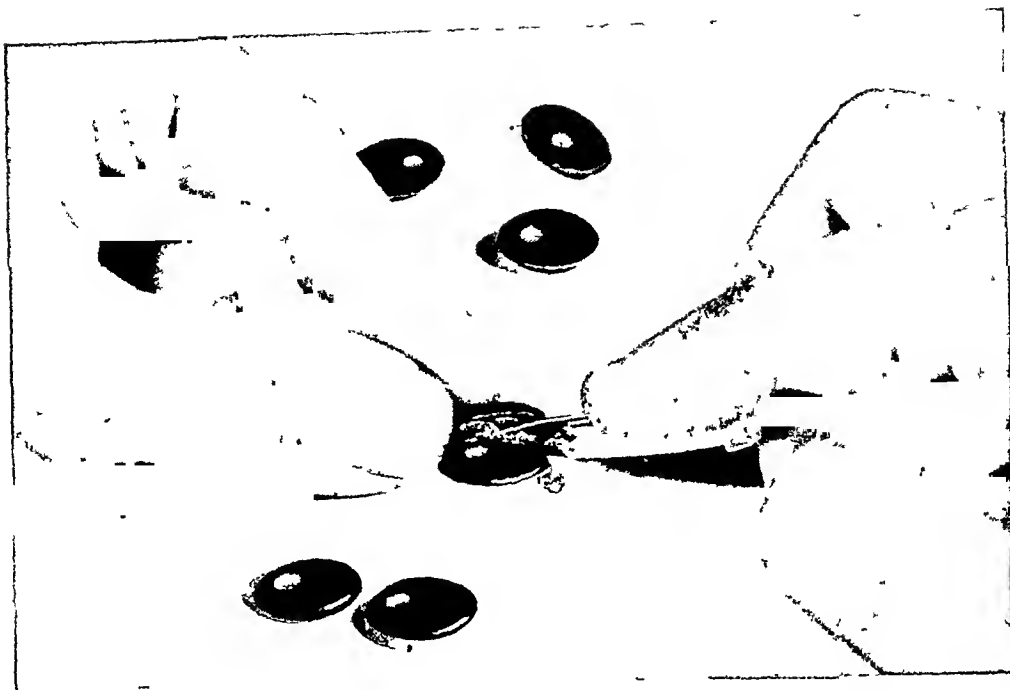
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turbance of water metabolism occur.

During the past ten years, the roentgenologic findings have been gradually clarified and classified consisting of:

1. In the small intestine—"Moulage Sign," dilatation, segmentation.
2. In the colon—Dilatation and redundancy.
3. In the gall bladder—Faint filling.
4. In the bony skeleton—Osteoporosis, deformity, and dwarfism.

Small Intestinal Findings:

Normally the valvulae conniventes which are present in decreased frequency from the duodenum to the ileum are clearly seen in the X-ray

film. In steatorrhea, however, they become coarser or ironed out. The wall outline seems softer than normal and may resemble a tube into which wax has been poured. This Dr. Kantor calls the "Moulage Sign." There may also be dilatation and segmentation of the small bowel with intervening areas of spasm. The emptying time of the small intestine is often prolonged.

The pathology which underlies the X-ray appearance is still as yet not definitely known. This is particularly important, in view of the fact that diseases other than "idiopathic steatorrhea" have been reported as producing similar X-ray findings. They have been reported in patients with

pellagra, chronic pancreatitis, carcinoma of the head of the pancreas, lymphosarcoma of the intestine or of the mesenteric lymph glands, as well as in gastro-colic fistula.

Colon Findings:

An interesting observation is that this disease is the only form of chronic diarrhea in which the colon is dilated instead of being narrowed. The dilatation is due to the gas formed by the fermentation of sugars which fail to be absorbed in the small intestine. Associated with this typical colonic dilatation is a moderate degree of redundancy.

Gall Bladder Findings:

Although the data is insufficient, there is some indication that failure of the gall bladder to visualize well is a characteristic roentgen finding during the acute phase of the disease.

Bone Changes:

In children, stunted growth has often been reported as the result of steatorrhea. In adults, there may be such changes as spontaneous fractures, bending of bones, un-united epiphysis, pain and tenderness over the bones and joints.

The author presents six cases of "idiopathic steatorrhea." Many of these patients were seen by other physicians and permitted to go on without a definite diagnosis being made from the clinical picture. In several instances, on reviewing the old films typical roentgenologic changes were noted. Adequate treatment, consisting of a banana and strawberry diet, accompanied by injections of the liver and vitamins, resulted in improvement. In one series of films, the improvement was demonstrated roentgenologically by the reappearance of the normal markings of the jejunum and the disappearance of a previously noted "Moulage Sign."

Henry H. Lerner, Boston, Mass.

EGGERS, CARL.

Cancer of the Gastro-Intestinal Canal. Bulletin of the New York Academy of Medicine. Vol. 14, No. 6, pp. 325-348, June, 1938.

Eggers gives a clear description of cancer in the gastro-intestinal tract. He emphasizes that in New York City about 6% are found in the esophagus, 33% in the stomach, 1/2% in the small intestines, 25% in the colon and sigmoid and 14% in the rectal sigmoid. Eggers stresses the importance of the preoperative treatment with administration of adequate quantities of fluids to overcome dehydration and toxemia. Preoperative precautions should be given to raise the lowered vitality. The results of Eggers operative experience in cancer and carcinoma of the sigmoid after 5 years show that 31% were still alive. In



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carcinoma of the sigmoid and rectum, 31% were still alive. The author stresses the importance of an early diagnosis of cancer which would improve the results of our treatment.

Franz J. Lust.

MAYER, EDGAR AND DWORKIN, MARTIN.

Roentgen and Light Therapy of Intestinal and Peritoneal Tuberculosis. Radiology, Vol. 31, No. 1, pp. 35-41, July, 1938.

The use of roentgen-ray and light radiation for treatment of intestinal and peritoneal tuberculosis is often productive of good results, warranting more general use of these

measures as adjuvants to rest and hygienic treatment. A trial of tumor dosage of X-ray under careful study is indicated in proliferative forms of intestinal and peritoneal tuberculosis that have not responded to smaller doses. With X-ray treatment, best results are obtained in hyperplastic and simple proliferative forms of intestinal and peritoneal tuberculosis, and especially when applied early in ascitic forms of peritoneal tuberculosis. With light therapy, both natural and artificial the ascitic and proliferative forms of peritoneal tuberculosis as well as the proliferative and ulcerative forms of intestinal tuberculosis

are generally responsive in patients not too critically ill.

Franz J. Lust, New York, N. Y.

GOTTLIEB, CHARLES AND REITMAN, NORMAN.

Leiomyosarcomatosis of the Small Intestine. Am. J. of Roent. and Radium Therapy, Vol. XLI, No. 2, March, 1939.

A case of multiple leiomyosarcoma of the small intestine is presented. This appears to be the first case of multiple leiomyosarcoma of the intestines to be reported. Leiomyosarcoma of the small intestine is a relatively rare tumor, occurring in one out of every 96 cases of small intestinal tumors. They may be divided roughly into an internal and external type. Although the diagnosis may be made clinically, there is no definite clinical syndrome, and the diagnosis is usually made by the pathologist.

Gottlieb and Reitman think that the roentgenological study of the gastro-intestinal tract is unsatisfactory as a rule. They show, however, roentgenograms on which some of the round masses in the small intestines can be detected. This report proves again the importance of roentgenological study of the small intestines.

Franz J. Lust, New York, N. Y.

HASEGAWA, TAKURO.

Influence of Splenectomy on the Alkalinity of Intestinal Juice. Arbeiten aus der medizinischen Fakultät Okayama, 6, 72-8, 1938.

The acidity of the intestinal secretions was studied in dogs provided with simple intestinal fistulae. Cholic acid administration produced a rise in pH. Splenectomy likewise resulted in an elevation of pH values, but the magnitudes of this rise and of the volume of secretion were not as great as with the cholic acid. Administration of spleen extract maintained the alkalinity at a normal value, although the pH was reduced subnormally. Bile acid exerted a similar effect.

Franklin Hollander.

AKERLUND, AKE.

Transparent Gas Containing Fissures in Gall Stones and Their Roentgenological Significance. Acta Radiologica. Vol. XIX, Fasc. 3, pp. 215-229, 30:IX, No. 109, 1938.

Star-shaped fissures in gall stones occur not only in dried specimens but also quite extensively during life when they usually contain fluid or semi fluid material and do not roentgenologically stand out against the tissues of the body. These cracks are of roentgenological interest only in

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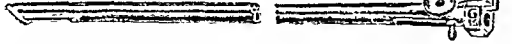
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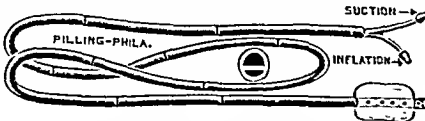
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the relatively rare cases where they are directly evident on the roentgen film due to striking transparency or when they bring about a decrease in the specific gravity of the concretum, a feature which comes to light in roentgenological sedimentation examinations. Both the great roentgenological transparency of the fissures and the low specific gravity of the stones as estimated on the fresh specimen (varying in Akerlund's material between 1,010 and 1,035 and thus being lower than even the specific gravity of pure cholesterolin) showed that in such rare cases the cracks contain gaseous substances probably arising from gas-producing bacteria or from other disintegration processes.

These transparent star-like fissures in the gall bladder region have up to the present attracted very little attention in roentgen diagnosis and cause of the occurrence of this new roentgen sign has never before been explained. However, gas-filled fissures within a gall stone, even if they are rare, may in certain cases make possible a diagnosis of gall stone when the concretum itself cannot be roentgenologically verified in any other way.

Franz J. Lust, New York, N. Y.

BAILEY, H.

Acute Dilatation of the Stomach.
Brit. Med. J., p. 434, March 4, 1939.

Acute dilatation of the stomach was first described by Kundrath in 1871 and Fagge in 1872. It is a common complication which may occur after any operation. Actual vomiting occurs relatively late and the condition should be recognized before vomiting occurs.

The stomach should be emptied and kept empty by constant drainage through a stomach tube (nasal type). Intravenous saline should be administered continuously. The patient's position need not be shifted. Patient may be allowed to drink but the ingested fluid is removed by the stomach tube. Eserine, 1/200 grain, may be given every four hours for 3 doses. The gastric tube is left in place for 36 hours before the stomach recovers tone.

HOYER, ANDREAS.

The Roentgen Diagnosis of Intestinal Obstruction. Acta Radiologica., Vol. XIX, Fasc. 5, 30:XI, No. 111, p. 409-432, 1938.

The author describes the roentgenologic symptoms of intestinal obstruction (without the contrast media). The significance of the amount and location of gas in the colon is stressed by Hoyer. He reports his findings in 46 acute abdominal cases in which he



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REPRINTS of the Editorial "Aids to Normal Bowel Function," "Amer. J. Dig. Dis., March, 1939; J. A. Bergen, M.D., will be supplied on request.

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was able to give a correct reply as to whether or not an intestinal obstruction was present. In the majority of the cases Hoyer was able to locate the accurate site of the lesion. It is important to know that we have certain normal (physiologic) fluid levels in the stomach, duodenum and terminal coil of the ileum, which should not be confounded with pathologic conditions.

Franz J. Lust.

NORGAARD, FLEMMING.

Peptic Ulcer of the Esophagus.
Acta Radiologica, XIX, 5, 458,
1938.

Primary diagnosis of peptic ulcer of the esophagus by roentgenological examination is much rarer than ought be expected, even considering the rarity of the affection. The author reports such a case, in which the diagnosis was established roentgenologically. It is important to repeat the examination if necessary several times and preferably during periods with markedly pronounced symptoms, or else under artificial provocation of such symptoms. (hard bread to swallow!!)

Franz J. Lust.

LUEDIN, MAX.

Lymphatic Hyperplasia of the Mucosa of the Stomach in Lymphatic Leukemia. Roentgenpraxis,
5, 11, 1816, 1933.

Lymphatic leukemia is able to involve the stomach to a great extent. A case is described in which the mucosal studies could be compared with the autopsy specimen. The infiltration of the mucosa is shown in the form of broad rugae. These irregular rugae can not be flattened out by palpation during the fluoroscopy. The histological examination confirmed the diagnosis in showing that the mucosa and the muscularis propria were infiltrated by lymphatic tissue.

Franz J. Lust.

OPPENHEIMER, ALBERT.

Acute Transient Intestinal Atony.
Am. J. Roent. and Rad. Therapy,
Vol. 41, No. 4, pp. 574-580, April,
1939.

In a well-illustrated, brief article, Dr. Oppenheimer describes the occurrence of dilatation of the colon in cases where the pathology was primarily either in the urinary tract or in the gall bladder.

The well-known observation that the colon often appears dilated and filled with gas in instances of disease of the genito-urinary tract, particularly calculi is reaffirmed by his findings. Studies performed on the gastro-intestinal tract during retrograde pyelography reveal that: (1) the

PRESENT VITAMIN STANDARDS AND UNITS

● Early in this decade the first International Standards of Reference and Units for vitamins defined in terms of definite quantities of the standard materials were tentatively adopted by the Permanent Commission on Biological Standardization of the League of Nations. At subsequent meetings this Commission has replaced certain of the original standard materials by the pure vitamins or preparations considered to be better adapted as standards of reference. However, the new units defined in terms of the new standards represent approximately the same biological activities as the original International Units.

Believing that the present units and the standards of reference upon which they are based will be of interest, they have been tabulated and defined:

Vitamin A

The standard of reference (1) is a solution of purified beta-carotene in an inert oil, of such concentration that one gram of solution contains 300 micrograms (0.300 mg.) of beta-carotene. The International Unit of vitamin A is the vitamin A activity of 2 mg. of the standard solution, or 0.6 micrograms of beta-carotene.

Vitamin B₁

The reference standard (2) is the International Standard preparation of thiamin chloride. The International Unit for vitamin B₁ is the antineuritic activity of three micrograms (3 μ) of the International Standard.

Vitamin C

The reference standard (1) for vitamin C is a specified sample of crystalline levo-

ascorbic acid. The International Unit for vitamin C is the vitamin C activity of 0.05 mg. of this standard.

Vitamin D

The reference standard (1) for vitamin D is a solution of irradiated ergosterol, prepared under specified conditions at the National Institute for Medical Research (London). The International Unit for vitamin D is the vitamin D activity of 1.0 mg. of this standard solution.

The International System of expressing vitamin values will undoubtedly soon become official for all authoritative agencies which concern themselves with the establishment of vitamin standards and units. Reference standards for riboflavin and nicotinic acid—both of which are of significance in human nutrition—have not been defined. However, the use of units such as micrograms or milligrams of the crystalline compounds to express riboflavin and nicotinic acid values is becoming increasingly prevalent.

The use of vitamin units of definite value permits correlation of various phases of vitamin research, particularly those phases relating to the vitamin contents of common foods and to the quantitative human requirement for these essential food factors. Although vitamin supplementation of the diet may be desirable under certain circumstances, it is apparent (3) that a well planned mixed diet is most suitable for supplying optimal quantities of the vitamins along with the other essential nutrients. The established vitamin values of canned foods (4) serve as an indication of their usefulness in formulating such diets.

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- (1) 1935 Nutrition Abstracts and Reviews, 4, 703
(2) 1938 League of Nations Bulletin of the Health Organization, 7, 882
(3) 1938 J. Am. Diet. Assn., 14, 1
1938 J. Am. Diet. Assn., 14, 8

- (4) 1935, J. Home Econ., 27, 638.
1935, J. Nutrition, 9, 667.
1938 J. Am. Med. Assn., 110, 650.
1938 Nutrition Abstracts and Reviews, 8, 281.

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stomach is dilated, the pylorus spastically closed; (2) that some of the loops of the small intestine are dilated, with diminution of the peristalsis, while other loops may be spastically contracted; and (3) that the colon is dilated and elongated.

From these findings, he concludes that the findings are due to irritation of a sensitive renal pelvis. This dilatation or stony disappears rapidly, indicating that the intestinal muscle itself was not damaged. The author maintains that this work is a confirmation of Alvarez's experiments in respect to the normalcy of intestinal muscular response in experimental paralytic ileus. As a result of these experiments, the author maintains that intestinal ileus may be produced by inhibitory impulses which originate in irritation of the peritoneum or the renal pelvis.

Henry H. Lerner, Boston, Mass.

BRUCE, G. G.

Diagnosis and Treatment of Acute Appendicitis in Children. Linct, p. 1247, June 3, 1939.

The paper constitutes a report on 467 consecutive operations in cases of acute appendicitis in children under the age of twelve years. The mortality was 1.9 per cent, all the deaths occurring in cases with perforated appendix with local or general peritonitis. Bruce finds at least five different types of clinical pictures which the child with acute appendicitis may present and warns against thinking of only a single set of symptoms. Immediate operation is advisable in children. It is essential to diagnose the condition before opening the abdomen and to operate quickly, gently and accurately.

M. H. F. Friedman, Detroit.

LINDER, FRITZ.

The Active Principles of the Small Intestine. Medicine in its Chemical Aspects. Bayer, Leverkusen, Germany, Vol. 3, p. 226, 1938.

A review dealing chiefly with the "hormones" reported present in the small intestine. Secretin, cholecystokin, inkretin, and hncemopoietin are dealt with but no mention is made of enterogstrone. The role of the small intestine as a detoxicating agent is stressed.

M. H. F. Friedman, Detroit.

BRAUCH, F.

Studien zur normalen und pathologischen Physiologie der Bewegungsvorgänge am menschlichen Magen. Ztschr. klin. Med., Vol. 134, p. 581, 1938.

No correlation was found between the state of the blood sugar level and

the gastric hunger movements in both normal and sick humans. The spontaneous movements of the empty stomach probably are not due to a fall in blood sugar level. During active gastric peristalsis there are neither the sensations of hunger or the abdominal rumblings. Gastric pain is usually correlated with alterations in the tonus of the gastric musculature but perhaps may also be associated with increased or decreased gastric peristalsis.

M. H. F. Friedman, Detroit.

MACY, I. G., REYNOLDS, L. AND SOUDERS, H. J.

The Effect of Carmine Upon the Gastro-Intestinal Motility of Children. Am. J. Physiol., Vol. 126, p. 75, May, 1939.

Seven healthy children, ages 7-11 years, were given 0.2 to 0.3 gm. carmine. The earmine reduced by 21 to 51 per cent the average emptying time of the stomach but the intestinal motility was decreased so that the total retention time of a barium meal was unaffected. The authors point out that since carmine is used as a marker for separating fecal units in metabolism studies, due consideration of its influence (decreased peptic and increased intestinal digestion phases) should be made.

M. H. F. Friedman, Detroit.

MORRISON, J. L., SHAY, H., RAVDIN, I. S. AND CAHOON, R.

Absorption of Glucose from the Stomach of the Dog. Proc. Soc. Exper. Biol. Med., Vol. 41, p. 131, May, 1939.

Contrary to what is believed by many, these workers present evidence that the stomach is capable of absorbing glucose. Using dogs under amylal anaesthesia, they found that isotonic solutions are not absorbed to any significant degree but that higher concentrations are definitely absorbed. The concentration of the glucose solution in the stomach apparently determines the rate of absorption.

M. H. F. Friedman, Detroit.

ROBINSON, LEON J.

Radiologic Gastro-Intestinal Studies in Epilepsy. Am. J. Psychiat., Vol. 95, p. 1095, March, 1939.

Röntgenographic studies were carried out on 100 patients with epilepsy. Examination was made immediately after giving barium sulfate and 6, 24, 48, and in some cases 72 hours later. 86 per cent of the patients had a normal gastro-intestinal series, 4 per cent had duodenal ulcer, and one patient had a gastric ulcer. It was concluded that there is no characteristic gastro-intestinal

pathology in epilepsy. The gastrointestinal auras present in 23 per cent of the epileptic patients did not depend on demonstrable abnormalities of the digestive tract.

M. H. F. Friedman, Detroit.

CONNOTATIONS

H. J. SIMS, M.D.

Denver, Colorado

The pancreas was first described by Wirsung in 1642.

In 1885, De Cereville performed what is now known as the first thoracoplasty. He resected segments of ribs over tuberculous cavities at the apex of the lung.

Durston described in 1670 the first case of tracheoesophageal fistula.

In 1812, Meckel discovered and described a diverticulum, now known by his name. He added that the structure of its inner layer was identical with that part of the intestine from which it arises.

In 1882, Cervello introduced paraldehyde.

Mereshinson recognized an emotional jaundice. He believed that, as a result of lowering the blood pressure in the liver, the tension in the small bile ducts became greater than that in the blood vessels.

Galen's textbook of anatomy appeared in 195 A.D. The platysma myoides, palpebral, palmaris, plantaris, and the interossei muscles of the hands and feet are described. Since it was unlawful at that time to dissect human bodies, it is believed much of Galen's information was gained by dissection of the Barbary Ape. It is more than possible that much of his knowledge was gained through the method of embalming as abdominal organs were removed through an abdominal incision and then embalmed and returned to the body. He gives no description of the brain; it is to be recalled that as the brain was removed through the nose, it was necessarily destroyed. The heart was never removed as it was assumed that the heart was an organ of necessity and immune to disease. Consequently, absence of pathology of the heart was noticed. Galen mentions a complete human skeleton being on display in Alexandria, the only one known to him.

Hotel Dieu is the favorite name for hospitals in France. Every city capable of supporting one or more hospitals has its Hotel Dieu. Its literal translation is: House of God.

Galen stated that inflammation of visible parts of the body offers no difficulty, but there is difficulty in recognizing it in hidden parts.

Boas made an attempt in 1889 to recover the duodenal contents through a tube. Hemmeter made a definite attempt to intubate the duodenum.

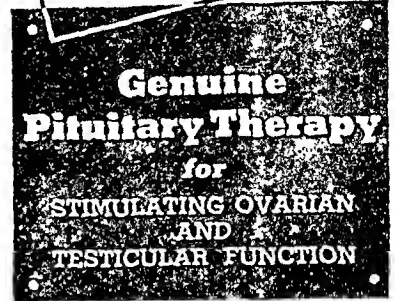
Turek insists on priority of this procedure; however, his primary intention was to outline the boundaries of the stomach by the aid of a pyrometer. Eihorn and Gross developed in 1909 the duodenal tube much as it is used today.

In 1868, Kussmaul attempted gastroscopy with a rigid tube but was unable to visualize the interior of the stomach. Micolicz was the originator of the modern instrument. In 1895, Rosenheim developed the new type of gastroscope.

It is believed that both the Greeks and the Egyptians successfully carried out operative procedures on hernia. However, Celsus in the first century, A.D., gave a fairly accurate description of a hernia and of the surgical technique for its relief. The origin of the word *hernia* is not known. It is believed that its inception dates from one of the vulgar terms used in reference to the genitalia, concerning which Celsus apologized in his writings. Celsus advised against surgery on hernia that did not cause pain. Historians visualize operations as being performed for cosmetic reasons only and not from any discomfort or complications which might be suffered. In the Baths of the Roman Clubs, where nude baths were taken, each Roman desired to exhibit the perfect body.

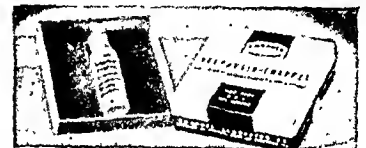
The origin of madstones is unknown. In the application of madstones to wounds it was directed that the flat surface of the stone be applied to the wound and maintained in position by bandages for several hours. The stone was then removed and placed in warm milk. If green bubbles appeared, it signified that the poison was being abstracted. This procedure was repeated until the green bubbles no longer appeared. There seems to have been a wide variety of madstones. One variety, a porous calcareous stone, was capable of absorbing its own weight in water and possessed unusual magic power. When fully saturated with water, the weight of the stone necessarily separated it from the wound. Oddly, the same discoloration and bubbles may be noted by boiling calcium carbonate gall stones in milk. Calculi and enteroliths were unusual prizes if they were discovered in a deer by an Indian. It is known that Indians artificially made madstones; the secret of the process was religiously guarded.

William Bull, born in 1710, was the first native born South Carolina physician. Other physicians preceded him but they were English immigrants. It is believed Dr. Jacob Lumbrazo, a Portuguese immigrant who was born in 1656 was the first Jewish physician in America.



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"Sevringhaus, E. L., "Endocrine Therapy in General Practice," 1938.



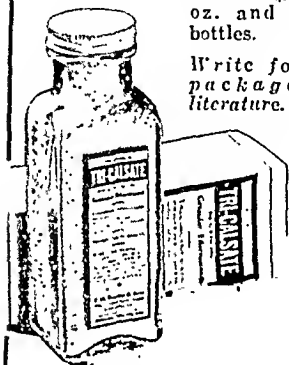
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BAKER, M. D.

A Statistical Note on Gastro-Intestinal Disorders in Infants.
Arch. Dis. Child., Vol. 14, p. 40, March, 1939.

Analysis is made of 1993 case records of children under the age of one year who were treated at the Alder Hey Children's Hospital, Liverpool. Of this number, 539 cases were classified as gastro-intestinal disorders. Of these 539, 45 per cent were within the expected weight range; 34 per cent were 20 to 40 per cent underweight, and 15 per cent were more than 40 per cent underweight. A latent infection was the suggested cause of the digestive disturbances in many cases. The incidence of "true summer diarrhea" was comparatively low. The diets of the infants under one year were found to be very unsatisfactory.

M. H. F. Friedman, Detroit.

HANEY, H. F., ROLEY, W. C. AND COLE, P. A.

The Effect of Bile on the Propulsive Motility of Thiry-Villa Loops in Dogs. *Am. J. Physiol.*, Vol. 126, p. 82, May, 1939.

A series of Thiry-Villa loops were prepared in dogs, the loops being about 12 cm. long. A small rubber sponge pellet was placed in the proximal end and the time taken for expulsion at the distal end noted. Dog's gall bladder bile when introduced at the proximal end markedly increase the rate of propulsion of the rubber pellet. That this effect was not due to the pH of the bile was shown by control experiments. The authors conclude that bile salts may play an important role in the normal regulation of the propulsive intestinal movements.

M. H. F. Friedman, Detroit.

ROBERTS, L. V.

Achlorhydria in Landry's Paralysis. *Brit. Med. J.*, p. 1084, May 27, 1939.

The cause of Landry's paralysis is not known but it is considered by some to be a striking form of acute

polyneuritis. The concurrence of polyneuritis with lack of free hydrochloric acid in the gastric juice makes Roberts' case of Landry's paralysis associated with achlorhydria of interest. Free HCl was shown only when the patient was fully recovered. Vitamin B₁, effective in some forms of polyneuritis and alcoholic neuritis, was not effective in the present case. Roberts believes there may have been a deficient formation or absorption of some other neurotropic factor.

M. H. F. Friedman, Detroit.

SHELDON, W. AND HALL, M.

The Apple Treatment in Infantile Diarrhea. *Arch. Dis. Child.*, Vol. 14, p. 43, March, 1933.

The apple treatment for diarrhea of children was practiced in England before 1775. Sheldon and Hall give their results of treatment in 36 babies, age range 9 weeks to 2 years. The infants were from lower income families and most of them were anemic, puny and undernourished. Apples were peeled, grated, and the wash fed. Even finely cut peel caused vomiting so care was taken to exclude the peelings. Tea was also given to keep the water intake level high. Most noticeable effects were lessening of toxemia, improvement in stools, and gain in weight. The treatment is not specific but is a valuable adjunct. It is best used in the persistent diarrhea associated with frequent passage of loose offensive stools.

M. H. F. Friedman, Detroit.

DOENGES, J. L.

Spirochetes in the Gastric Glands of Macacus Rhesus and of Man Without Related Disease. *Arch. Pathol.*, Vol. 27, p. 463, March, 1939.

Spirochetes were found in the gastric glands of 43 per cent of 242 human stomachs examined in routine autopsies and in 100 per cent of a series of 43 rhesus monkeys. Reports in the literature of the presence of spirochetes in both dogs' and cats' stomachs are numerous and probably the spirochete is present in 100 per cent of rats. However, spirochete infection is species specific, it is absent in mice and *Cebus fatuellus* (monkey). The pathogenicity is low. The infection centres in the parietal cell. The question still remaining to be answered is whether the spirochete of these animals (cat, dog, monkey and rat) can be ignored in physiologic and pathologic studies of the stomach.

M. H. F. Friedman, Detroit.

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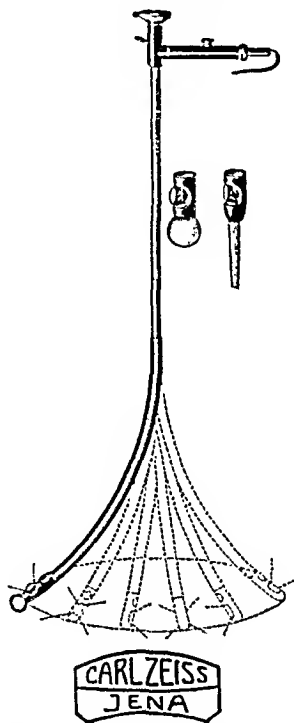
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1. Einsel, I. H., Adams, W. L. and Meyers, V. C., Am. J. Dig. Dis., 1:513, 1934.

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*Windwer and Matzner, *Am. Jl. Dig. Dis.* 5:743, 1939.

NOTE:

The gelatine used in this study was plain Knox Gelatine (U.S.P.) which assays 85% protein and which should not be confused either with inferior grades of gelatine or with sugar-laden dessert powders, for these latter products will not achieve the desired effects. When you desire pure U.S.P. Gelatine, be sure to specify KNOX. Your hospital can get it on order.

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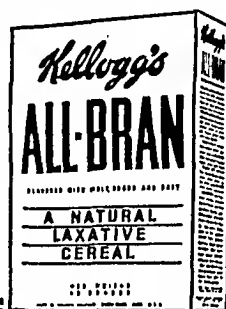
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The Etiology, Diagnosis and Medical Management of Pancreatic Disease

By

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BALTIMORE, MARYLAND

ETIOLOGY AND PATHOLOGY

THE diagnosis of diseases of the pancreas continues to be one of the most difficult problems in internal medicine; the reasons for this are not far to seek, since the organ is either difficult or impossible to palpate unless greatly swollen; even then it is not always easy to differentiate it from other organs. We are all familiar with the puzzle confronting the surgeon at operation when he must inspect and palpate the pancreas and it presents no picture of fat necrosis nor evidence of hemorrhagic necrosis. Last but not least, the methods and tests for the secretory power of this organ are in most instances anything but convincingly adequate, particularly in the early stages of chronic disease.

The most urgent problem to be dealt with in disease of this organ is the overwhelming mortality in acute pancreatic necrosis, or as some authors prefer to term it, acute hemorrhagic necrosis. Extensive and valuable experimental work has been carried out during the past few years, in an earnest endeavor to find the etiologic factor or factors, and in the light of this knowledge prepare new methods of approach which may materially aid in successful medical and surgical measures. Certainly a better understanding of the disease is a pressing duty laid upon the profession.

Everyone is familiar with the fact that the pancreas is indispensable to life, that it is in close proximity to the vital celiac nerve plexus, and that because it is in an area where absorption of toxic chemical products occurs with unusual facility, there is a limit to the scope of surgical treatment.

Outstanding problems to be solved are the causative factors in sudden extensive necrosis of the pancreas, and the reason why so rapid a process causes death.

The results of a very comprehensive and illuminating research have recently been presented by Dragstedt, Haymond and Ellis (1), and these are well worth pondering. The authors are of the opinion that about sixty per cent of the cases of acute pancreatitis necrosis in man arise in patients with antecedent chronic biliary tract disease. Of these, it is likely that ten per cent develop a common channel as a result of the impaction of a gall stone in the ampulla; a majority of the remainder develop a similar continuous channel through spasm of the sphincter of Oddi or edema of the papilla. Bile produces necrosis of the pancreatic parenchyma because of the local cytolytic and destructive properties of the bile salts, and not through activation of the intraductal trypsinogen of the pancreatic juice. The toxic effect of the bile salts is neutralized by the proteins of the blood serum so that hemorrhage and exudation are protective phenomena. The digestion of the protective proteins of the serum by the proteolytic enzymes of the pancreatic juice frees the bile salts for further destructive action,

and this probably accounts for the greater susceptibility of the pancreas to biliary necrosis than is found for other glandular organs. There is no good evidence that the intraductal or intraglandular activation of trypsinogen will cause self-digestion of the pancreas. Active trypsin was found to be incapable of digesting living tissue. It is probable that trypsin has no corrosive properties in itself which would injure living cells and that it acts only as a catalyst in facilitating the hydrolysis of proteins by the alkali of the pancreatic juice. The locally destructive action of pancreatic juice is dependent on its concentration of alkali just as the corrosive effect of gastric juice is dependent on its concentration of free acid.

It is probable that irrespective of whether the necrosis of the pancreas is due to the invasion of bile, to trauma, to vascular injury or to infection, the cause of the resulting toxemia is the same. Inactive pancreatic juice was found to be non-toxic if allowed to flow into the free peritoneal cavity, and it is probable that in acute pancreatitis the fat necrosis is due more to the destructive action of bile than to that of pancreatic juice. The digestion of the fat is brought about by the latter secretion. The intraperitoneal injection of actively proteolytic juice was found to be no more toxic than the intraductal secretion if bacterial contamination was avoided.

It is most helpful to learn that the uncontaminated pancreas of each of ten living, normal adult rabbits yielded positive bacterial cultures. In 13 of 17 dogs similarly examined, bacteria of various types were found in the uncontaminated pancreas. These bacteria were similar to those common to the intestinal tract. *B. Welchii* was especially prevalent. The toxemia resulting from experimental *in vivo* autolysis of the pancreas is chiefly due to the presence of these organisms, which proliferate in the necrotic tissue. It is possible that the toxin of *B. Welchii* may contribute to the toxic effect, but it seems probable that the major part of the toxemia is due to the group of proteinogenous amines and similar substances arising from the bacterial decomposition of proteins or their split products.

A recent valuable contribution on the subject of acute hemorrhagic pancreatitis has been presented by Rich and Duff (2); they take sharp issue in several instances with Dragstedt and other investigators regarding some of the etiologic factors which produce this serious condition, and state in their summary that in human and experimental hemorrhagic pancreatitis there occurs a constant and specific vascular lesion, characterized by rapid necrosis of the walls of the arteries and veins; that the pancreatic hemorrhage results from the rupture of the necrotic vessels; further, this vascular necrosis is the direct result of the action of pancreatic juice upon the walls of the vessels, and the agent in the juice responsible for the

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necrosis is the tryptic ferment. The activation of trypsinogen by enterokinase is not necessary for the production of the vascular necrosis.

The majority of cases of hemorrhagic pancreatitis result from partial obstruction to the outflow of the secretion, causing distention and rupture of acini and ductules behind the obstruction, with resulting escape of pancreatic juice into the interstitial tissue. If the escaping juice is rich in tryptic ferment and comes into contact with arteries and veins, their walls will be destroyed, and extensive or localized hemorrhage will occur, depending upon the size of the affected vessels. If no arteries or veins are present in the vicinity of the acinar rupture, or if the escaping secretion has a low tryptic power, fat necrosis produced by the lipase of the juice, may be the only result.

A very important point is stressed in the statement that the rupture of dilated, thinned-out acini behind an obstruction is particularly liable to occur during the periods of increased pressure within the system resulting from stimuli which greatly increase the production of secretion (e.g., a large meal, or the ingestion of alcohol).

These investigators differ widely with the views held by many other authorities, for they state that while the underlying obstruction in some cases of hemorrhagic pancreatitis is caused by a gall stone lodged at or near the ampulla of Vater, in most cases the main pancreatic duct is unobstructed, the obstruction being situated in branches of the duct within the pancreas. They emphasize the fact that in their experience retrojection of bile into the pancreatic duct is an infrequent cause of hemorrhagic pancreatitis, and proved cases in the literature are scarce.

They now offer the rather novel idea that metaplasia of the epithelium of the branches of the pancreatic duct, leading to partial obstruction and consequent dilatation of the acini and ductules behind the obstruction, is a very frequent occurrence, having been found in their routine sections in 18.6 per cent of 150 consecutive autopsies on individuals over 25 years of age. Rupture of the distended acini behind the obstructing metaplasia also occurs frequently, but in most instances the resulting damage is limited to focal fat necroses or small hemorrhages. There is evidence that acute attacks of severe epigastric pain may be associated with these accidents. The authors emphasize the fact that metaplasia of duct epithelium with associated acinar dilatation was found in the routine sections in 13 of 24 cases of hemorrhagic pancreatitis. It is their belief that this form of duct obstruction leading to acinar rupture and escape of secretion plays an important role in the pathogenesis of many cases of hemorrhagic pancreatitis, though any of the numerous causes of duct obstruction may of course lead to the same result.

The overwhelmingly practical value of the above investigations is at once apparent.

SYMPTOMATOLOGY AND DIAGNOSIS

In an excellent clinical study of acute pancreatitis, Cole (3) calls attention to the classification of this entity, differentiating the acute edematous or interstitial type from that group which is divided into the hemorrhagic, necrotic or suppurative; this latter group is of the fulminating type with a high mortality approaching fifty per cent, while in the former group mortality is five to ten per cent. There is yet another

type, chronic pancreatitis, which is characterized by induration of the head of the pancreas and frequently occurs in patients harboring gall bladder disease and other inflammatory conditions within the abdomen.

The outbreaks in acute hemorrhagic or necrotic pancreatitis are sudden and violent, usually appearing after a heavy meal or the ingestion of a large amount of alcohol, the antecedent history being that of a healthy individual. The pain is usually in the epigastric area, is in most cases agonizing, and very often leads one to suspect the rupture of one of the abdominal organs, since nausea and vomiting occur and after a short period the pulse becomes rapid and may be thready. In a few hours there may appear signs of shock and collapse, the blood pressure drops to a low point, and cyanosis is of outstanding prominence and significance. The pain may radiate to the right or left upper quadrant or through to the back. The temperature is at the outset subnormal, though within twenty-four to thirty-six hours it is likely to rise to 100-101 degrees Fahrenheit. Generalized abdominal sensitiveness is noted, but tenderness is most marked in the epigastric area, and muscle spasm in varying degree may or may not be a salient feature.

These patients give evidence of a toxic state; the leucocyte is usually between 15,000 and 25,000, though in this regard great variation may be noted. In grave cases the symptoms increase in severity and a critical state is likely to supervene; if this is due to suppuration the fever may reach 103-104 degrees Fahrenheit, and there is usually a corresponding rise in the leucocytosis; when such a picture is presented we must be very suspicious of abscess formation, which gives a strong indication for operative interference.

A mass will on occasion be palpated; this means that the organ is considerably enlarged. When the organ is closely inspected there may be evidence of changes; hemorrhagic, diffuse or local in character, or simply localized necrotic areas. Serous fluid is most often encountered in the abdominal cavity, and usually there will be seen areas of fat necrosis in the peritoneum and omentum.

In cases of acute edematous or interstitial pancreatitis, we meet with practically the same symptom-complex as above described, though of much less intensity. It should be mentioned that in a fair number of all cases of acute pancreatitis, jaundice in greater or less degree is present; if the common duct is blocked by a stone, an unusual occurrence in such cases, the jaundice may be quite deep.

One should always remember that the symptoms due to gall bladder disease—so frequently present in either of the types—may mask the signs and symptoms of the pancreatitis. The striking difference between the interstitial type and the hemorrhagic is the likelihood of the former subsiding two or three days after bed-rest, careful diet and fluids in proper amount, have been applied. A tumor mass is usually present; fluid in the abdominal cavity is rarely observed; but fat necrosis is likely to be noted and may persist for several weeks.

It is not at all unusual in these cases for one to be deceived as to the true diagnosis because the symptoms in hemorrhagic or suppurative pancreatitis—pain, collapse—do very greatly simulate those of perforated duodenal or gastric ulcer. In most instances, however, the pulse is much more rapid in pancreatitis than in

a recently perforated ulcer, and cyanosis is quite likely to be outstanding. As to hemorrhage in the case of ulcer, we are likely to witness a hematemesis; and whereas in the bleeding ulcer there is likely to be shown a considerable fall soon after the hemorrhage, the red cell count in acute pancreatitis will be elevated. Difficulty may be encountered in the differential diagnosis between acute interstitial pancreatitis and acute cholecystitis because both conditions may be present. One important and helpful point is the fact that in pancreatitis the tenderness noted in the epigastrium is likely to extend to the left across the upper abdomen.

In acute edematous pancreatitis the infrequency of glycosuria is rather striking, while in the hemorrhagic and necrotic types the elevated fasting blood sugar is a rather consistent finding.

During the past few years various observers (4) have been impressed with the value of the blood amylase test as a dependable diagnostic procedure in the diagnosis of acute pancreatitis. It has been satisfactorily demonstrated that there is an increase in blood amylase only in acute pancreatitis. The test is reliable in both forms, though normal or low readings, if they do occur, are more likely to be found in the fulminating type. The level rises to 150 from its normal 90 in a very few hours, and may reach 1000 after one or two days, following which there is a gradual decrease until the normal is reached; this may be two or three days after the disappearance of symptoms, though it has at times been observed that the level of blood amylase may return to normal many days before the symptoms subside. If a secondary exacerbation occurs there may again be an increase in blood amylase.

It has been asserted (5) that urinary diastase has equal diagnostic value with blood amylase, and Gray and Smogyi (6) state that although there is more amylase in the urine than in the blood, there is a greater individual variation in the same patient. As a rule the urinary amylase remains elevated twenty-four hours longer than the blood amylase and is lowered by renal disease.

The value of this test is practically nil in carcinoma of the pancreas and chronic pancreatitis, while it is positive in about fifty per cent of cases of pancreatic cyst. One may have difficulty in interpreting a low blood amylase reading; and while fibrosis and atrophy of the gland may account for this finding, yet it has been asserted by Smogyi (7) that the low readings may be due to hepatic disease.

There is no doubt that a conservative attitude is indicated during the acute stage of interstitial pancreatitis. Because of persistent vomiting in many cases, with consequent loss of fluid, the administration of large amounts of fluid in the way of subcutaneous saline and intravenous glucose is an urgent need, and will prove of inestimable value. Inasmuch as operative interference is usually directed toward the gall bladder disease, it is quite apparent that more satisfactory results will be the outcome if one awaits the subsidence of acute symptoms, thus also allowing the blood amylase to return to normal.

Most surgeons are agreed that the operation indicated in the great majority of cases is cholecystectomy; however, a marked disagreement exists regarding the moment of surgical attack in acute hemorrhagic or necrotic pancreatitis. Those of the radical

school advise operation as soon as possible after shock has been overcome; those of the conservative group feel that mortality will be greatly lessened if operation is delayed until the more acute state has subsided. It should be stated that at times it is impossible to differentiate between acute pancreatitis and other abdominal catastrophes, and in such circumstances it would seem that exploratory laparotomy is the avenue of choice; if there is found a suppurative pancreatitis, drainage of the abscess is indicated.

The subject of low-grade chronic pancreatitis is one which interests us all, and I am convinced that because of the lack of specificity of symptoms and the inadequate methods of investigation, we continually fail to recognize the condition as a causative factor in many cases presenting persistent abdominal symptoms, either outstanding or mild—such as pain (varied in character), fullness and distress, "gas," possibly nausea with occasional vomiting, and types of discomfort difficult for the patient to describe.

In a very timely and comprehensive presentation dealing with diseases of the pancreas, T. R. Brown (8) poses and answers two very pertinent questions: What do we diagnose sometimes correctly and sometimes incorrectly? The relative parities—pancreatic cyst, pancreatic carcinoma, acute pancreatitis. What do we almost always fail to diagnose? Practically all cases of the much more common chronic and mild subacute pancreatitis, and, in all probability, the major proportion of the functional disturbances.

Many individuals of middle or later life, presenting vague upper abdominal syndromes are unquestionably suffering from a chronic pancreatitis; the condition probably represents either a sclerosis or a low grade of infection which may originate from a diseased gall bladder. It has been suggested that the most common source is gastritis, or duodenitis, which may spread through the lymphatic channels; or on occasion it may represent a direct extension from disease in the vicinity such as peptic ulcer or cholecystitis; again, we have all witnessed definite cases of perforation of peptic ulcer into the pancreas. Aids to arousing suspicion of disease of this organ may appear in the form of alimentary glycosuria, changes in the stool—preferably with the patient on a Schmidt diet—with abnormal amounts of undigested fat or starch or meat fibres; a steatorrhea with bulky stools, excessive fat, offensive odor; a true azotorrhea or a true butter stool with more than one-half the ingested fat unabsorbed, and of this, fifty to sixty per cent in the form of neutral fat.

There can be no doubt that marked disturbance in fat digestion, diarrhea, the absence of jaundice, are very suggestive of pancreatic disease, because all of the fat-splitting ferment is found in the pancreatic secretion, with only minimal amounts in the gastric contents or in the intestinal juice; even with this information, however, one cannot be absolutely certain of the diagnosis because of a number of variables; that is, the differences in the motor and absorptive powers of the intestine, the possibility of vicarious enzymes from other sources, and possibly the effect of enzymes of bacterial origin, all of which confuse the picture.

It is essential that in dealing with diseases of the pancreas we realize that among the substances in the chyme which exert the greatest secretagogue effect

upon the pancreas are meat extracts, protein derivatives, acids, fats, fatty acids, soaps and water; in this regard it is most interesting and helpful to know that Pavlov has demonstrated a psychic element in the control of pancreatic secretion. Though the effect is much less than in the case of gastric secretion, sham feeding was found to increase very definitely the pancreatic flow.

The consensus of opinion of the great majority of authorities is that the estimation of pancreatic ferments in the duodenal contents and stool is, from the standpoint of diagnosis of disease of the pancreas, quite valueless. When the ferments are markedly diminished or absent the diagnosis is so self-evident that laboratory tests are as a rule not needed.

MEDICAL TREATMENT

When one ponders the underlying pathology of chronic pancreatitis it is readily apparent that therapy must of necessity be symptomatic and in a way truly empiric; support of the validity of this statement is found in the fact that the outstanding text-books of medical therapy fail even to mention the subject. However, patients who harbor this condition do consult us, and it is necessary to prescribe treatment; I shall therefore present an outline of the therapy which would seem to apply in these cases.

As to hygiene, one takes into consideration environment, occupation, mode of life; in short, all circumstances surrounding the patient's existence. Proper vacation, relaxation and recreation, or rest, are urged. Every effort is exerted to discover and eradicate any possible focus of infection.

The type of diet is dependent in great degree upon the urgency or mildness of the symptoms;—if marked complaint is made of "gas," discomfort, and the usual galaxy of various uncomfortable sensations, I prescribe a soft puree diet, properly balanced, and with particular attention to caloric sufficiency; it is to be noted that many of these cases are associated with hepato-biliary disease, and the diet is therefore largely based upon this knowledge. Fats in the form of the "natural fats" such as cream, butter, eggs and olive oil, are allowed in moderation; care is always exercised, however, to interdict the synthetic and cooked fats, likewise fried, greasy foods. An endeavor is made to increase gradually the type and variety of food until a general well-balanced diet is being used without untoward dyspeptic symptoms.

As to medicine, I always prescribe pancreatin; but since it is questionable as to just how potent is the particular supply given the patient, this is a problem difficult to solve. Inasmuch as the biliary tract carries so often an accompanying lesion, it is my practice to give dehydrocholic acid known as Deeholin and Procholon, or ketocholanic acid, the trade name of which is Ketochol. Spasticity of the ducts and intestine is almost always present, so antispasmodics such as belladonna, atropine, Syntropan, Trasentin, Novatropine and Bellafoline, in conjunction with a barbiturate (preferably in the form of phenobarbital), have given help in many cases. Alkalies—combinations of aluminum hydroxide and kaolin—or dilute hydrochloric acid, are used according to the indications in the individual case. Hematinics and various vitamins individually or in different combinations are administered when occasion seems to demand.

The bowel condition is controlled by various remedies; at times the salines, magnesia in different forms, the oleaginous preparations, cascara; and the simple pills such as Lady Webster, Lapactic or Alophen often prove very successful. Oil retention enemas on occasion have been most useful.

Should the symptoms be more or less acute with abdominal distention, nausea and vomiting, one may apply continuous intraduodenal suction siphonage, for helpful knowledge is sometimes obtained by studying the duodenal content for bile pigment, cholesterol crystals, pus cells and pancreatic enzymes. The appropriate fluids should be administered intravenously and subcutaneously. Depending upon urinary and blood estimations for sugar, insulin is given when and in the dosage indicated. It has been suggested that B. Welchii serum may be tried by slow infusion after sensitization tests.

I believe that in this field one of the outstanding contributions of recent years is that relating to lipocaic, by Dragstedt and his associates (9). After a very exhaustive research they concluded that "a specific substance has been obtained in fat-free alcoholic extracts of beef pancreas; that on oral administration to depancreatized dogs treated with insulin this substance permits survival and prevents and relieves fatty degeneration and infiltration of the liver in these animals. This substance, for which the name "lipocaic" is suggested, is believed to be a new hormone that is concerned in some way with the normal transport and utilization of fat."

It has been asserted that whereas in the early, pre-insulin days the diabetic patient died of acidosis, he now dies of coronary disease or diabetic gangrene. Because of his studies, Dragstedt (10) now inquires as to whether this means that many diabetics suffer from not only an insulin deficiency but also from a deficiency of lipocaic which manifests itself in a disturbance in fat utilization, with the deposition of fat in the liver and in more chronic cases in the sub-endothelial layers of the arteries.

Goodpasture and his associates (11) have recently presented what appears to be an excellent addition to our present knowledge of lipocaic; the work concerns a liver function test as a method of assay of lipocaic, and their conclusions are enlightening:

(1) Impaired liver function as evidenced by abnormal retention of bromsulphalein has been found in the large majority of insulin-treated depancreatized dogs that develop fatty infiltration of the liver.

(2) The disturbance in liver function has been found to be roughly proportionate to the amount of fatty infiltration and to respond to lipocaic therapy more rapidly. Accordingly the bromsulphalein test is suggested as an additional criterion of lipocaic deficiency in depancreatized dogs and as an aid in the assay of pancreas fractions for this substance.

Lastly, in regard to this very important hormone, I present a most illuminating report by Rosenberg (12) proving conclusively the efficacy of lipocaic in the treatment of a case showing fatty metamorphosis of the liver: An obese woman was operated because of ovarian disease; the surgeon examined the liver and found it enlarged, grossly fatty, yellowish and mottled. A section of the liver was removed for biopsy and fixed in Zenker's solution. Later a most meticulous

histologic examination of the specimen was instituted with the diagnosis: "Marked fatty metamorphosis of the liver." The patient was given treatment with lipocaine for some weeks. Several weeks after this treatment was instituted she developed severe attacks of biliary colic and operation was imperative. The surgeon reported that the liver was remarkably different from its earlier appearance. Whereas it had been yellowish, it was now uniformly reddish brown in color, and normal in size and consistency. A specimen of the liver was again obtained and preserved in formalin. Diagnosis: "Slight fatty metamorphosis of the liver."

Rosenberg's conclusion was that this case constituted a proved instance of recovery from fatty metamorphosis of the liver associated with diabetes mellitus, following treatment with lipocaine.

CARCINOMA

Carcinoma of the pancreas, while not a common disease, is of such frequency and import that it should receive serious consideration in every patient who consults us because of abdominal symptoms. Graham (13) has pointed out the most likely points of origin of the growth: "—an area having a radius of not more than 0.5 cm., a carcinoma may arise in any one of the following structures: (1) the ampulla of Vater; (2) the end of the common bile duct; (3) the end of the duct of Wirsung; (4) the glandular tissue at the head of the pancreas; and (5) the duodenal mucous membrane covering the biliary papilla." One must of course remember that carcinoma can and does occur in other parts of the pancreas, in which case jaundice may be absent throughout or only during the last stage of the disease.

More men than women are afflicted, in the ratio of about two or three to one, and the age in by far the greater percentage—80 to 85 per cent—ranges from forty to seventy years. The clinical course of these patients really has great similarity; an individual—most likely a man—presents himself with the story of having had persistent dyspeptic symptoms for some weeks or months during which time there has been noted considerable loss in weight; in some instances the loss has been quite rapid; there has been gradually developing a jaundice (present in most cases) which not only persists but increases in intensity; furthermore, with his dyspeptic symptoms of fullness, distress, "gas" and other untoward sensations, pain has been very annoying, and does not yield to treatment. The type of pain varies greatly and has no diagnostic importance; as to location of pain, this will vary; it may be localized in the epigastric area, radiate in various directions, or be referred through to the back or up to the right shoulder; again, it may be noted in the umbilical area or over the entire upper or lower abdomen. The pain may be constant and aching, or remittent, intermittent, and of a colicky nature; in severity it is variable, though often quite intense, requiring narcotic control.

The state of the bowel varies, and has no diagnostic significance; however, constipation is more frequent than diarrhea or a normal state.

Nausea and vomiting are usually noted during some stage of the disease, and cases have been reported wherein a pyloric obstruction has been brought about

by pressure on the pylorus due to an encroachment by the advancing pancreatic tumor mass. The duration of symptoms is extremely variable, ranging from a few weeks to two or three years; an average, however, would be about five or six months. The patient's past and the family history may yield no information of diagnostic value.

A careful palpatory search is instituted for an enlarged liver, which is usually discoverable in fifty to sixty per cent of cases, while epigastric tumor will be palpable in thirty to fifty per cent, and one should always endeavor to ascertain whether the gall bladder is distended; in this regard there seems to be a wide divergence reported by various authors, ranging from fifteen to eighty per cent.

Abdominal tenderness, dilated vessels in the abdominal wall, ascites and edema have been reported, especially when the disease was far advanced.

In the absence of jaundice the urinary findings are of no particular value, but bile is usually found in most of the jaundiced cases. As to the stools, occult blood is present in quite a large percentage, while gross blood is infrequently encountered; of course when the common duct is occluded acholic stools appear; the gastric acidity is most likely to show a hypochlorhydria or achylia gastrica.

The blood shows nothing of diagnostic value, a moderate to severe anemia being present in most cases; roentgenologic examinations are also valueless as a rule, though useful findings have been reported in a small percentage of cases.

A final word of warning may be given in regard to the possibility of temporary remission of the jaundice, and diminution in severity of symptoms; such instances, if we are not wary, may deceive us and lead to a reversal of our originally correct diagnosis.

Ransom (14) stated that Courvoisier's law was of relatively little value in making a correct diagnosis prior to operation, but that the law was of considerable value to the surgeon at the time of laparotomy, as it indicated the type of duct obstruction which was present, and the operative findings proved the law to be accurate in over eighty per cent of the cases.

Mention should be made of the other tumor entities of the pancreas; they are, tumors of the islets of Langerhans, and pancreatic cysts, the latter consisting of cystadenomata, retention cysts, and pseudo-cysts. The last are not situated in the substance of the pancreas, but in the immediate neighborhood, usually in the lesser sac of the peritoneum which lies directly in front of the pancreas. The chief causes of pseudo-cysts are previous attacks of acute necrosis and injury to the pancreas from trauma. There is no symptom-complex indicative of these growths, the symptoms usually simulating those of chronic pancreatitis.

Boyd (15) presents a very interesting suggestion, that chronic interstitial pancreatitis is frequently associated with carcinoma of the pancreas; whether this should be regarded as a cause or an effect it is difficult to say. As in the case of the liver, it is possible that compensatory hypertrophy of the parenchyma consequent upon fibrosis may be the starting point of carcinoma.

The mode of therapy in tumors of the pancreas is

surgery, which in many instances must needs be palliative. However, that phase of treatment is not within the scope of this paper. In this presentation

the endeavor has been to set before you an outline of the present-day conception of the etiology, diagnosis and therapy of diseases of the pancreas.

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The Activity of the Lower Part of the Ileum of the Dog in Relation to the Ingestion of Food

By

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and

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MUCH has been written about reflex phenomena in the gastro-intestinal tract. Reflexes affecting the activity of the intestine have been described with the receptor element in such divergent structures as the eye, Daniélopou, Simici and Dimitriu (1), 1925, the parietal peritoneum, various skin areas, King (2), 1924, the kidney, Piotet (3), 1934, and the testes, Cannon and Murphy (4), 1907. It has even been suggested that stimulation of any afferent nerve may reflexly affect the activity of the intestine, Lehmann (5), 1913.

Two things are common to all these reflexes: firstly, they are all abolished by section of the splanchnic nerves, and secondly, they are all inhibitory in character.

In contradistinction to the large number of inhibitory reflexes, only two motor reflexes have been described, the gastro-ileac reflex and the gastro-colic reflex. Both are concerned with the ingestion of food.

Hertz (6) credits Cash (7) in 1886 with having first made the observation that the taking of food is followed by increased activity in the lower part of the ileum. Macewen (8), 1904, noted in a patient who had a large hiatus in the right iliac fossa that the activity of the ileum was increased after eating. Hertz, 1913, applied the term gastro-ileac reflex to the motor response to feeding in the lower part of the ileum. He studied the reflex by giving a small amount of an opaque substance to a human subject, observing the

abdomen with a fluoroscope until the meal reached the lower part of the ileum, then asking the subject to eat a meal. He observed a very rapid increase in activity in the lower part of the ileum. Short (9), 1919, observed in a patient with a large cecal fistula that the taking of food was followed within one and a half to four minutes by the discharge of chyme through the ileocecal valve.

In the experimental field, Hinrichsen and Ivy (10), 1931, made a study of the activity of the lower part of the ileum and the ileocecal sphincter in the dog. They concluded that the feeding reflex is a definite phenomenon, that excitation of the duodenum by food from the stomach is the most important exciting factor, that previous fasting is necessary to permit of the best responses to feeding and that a response does not occur if the animal is merely shown the meal without being permitted to eat.

Puestow (11), 1931, was unable to satisfy himself that increased activity in isolated segments of the ileum of the dog occurred after feeding.

Castleton (12), 1934, however, noted a fairly regular motor response in the ileum of the dog in exteriorized loops in continuity.

Zollner (13), 1938, has recently made a roentgenologic study of the activity of the lower part of the ileum in man in response to feeding. He noted that a motor response occurred after the ingestion of a fatty meal, but no response occurred if a carbohydrate meal were eaten.

The present study was undertaken with several objects in mind. The principal object was to study the

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motor response in the ileum to feeding with reference to its mediation. In the present state of knowledge, there does not appear to be any direct evidence that this response is reflex in character at all, nor have any studies been made to determine the pathways of the hypothetic reflex arc. A second object of the study was to learn something of the activity of the empty ileum of the fasting animal, a subject about which little has been written, perhaps for the reason that the two methods which have been used by the majority of workers for studying intestinal activity, namely the Thiry-Vella fistula and the roentgen ray, do not permit of such a study. Finally, it was thought that by studying a pure motor response of this character some light might be thrown on the physiologic function of the motor nerves of the intestine. It is a striking fact that, as far as could be found in the literature, there has not been a convincing demonstration that the vagi, which are believed to be the motor nerves of the small intestine, play any part in mediating motor reflexes.

METHODS

It was apparent that the use of Thiry-Vella loops was unsuited to the present study for two reasons.

First, these loops do not share in the normal physiologic activity of the rest of the intestine, namely in the transport and digestion of food residues. This fact would obviously have defeated the aims of the investigation since it was the effect of the presence or absence of food residues on intestinal activity which we wished to study. Second, to record the activity of these loops it is necessary to introduce some form of balloon into the lumen of the intestine, which even at a pressure as low as 3 cm. of water stimulates activity.

Roentgenologic studies appeared to be unsuitable for a similar reason, namely that in order clearly to visualize the intestine it is necessary to introduce an opaque substance into the lumen with a consequent excitatory effect.

The desiderata of the suitable preparation appeared to be the following: The method should involve no breach in the continuity of the bowel, no introduction of foreign bodies into the bowel and finally no interference with the health of the animal in order that day to day observations could be made over a reasonable period of time.

The preparation which appeared to fulfill these requirements was an exteriorized loop of ileum in continuity, with mesenteric blood and nerve supply intact. Such a preparation has been used by Biehl (14) for the study of intestinal contents, by Castleton (12) for the study of the activity of the small intestine and by Wagensteen (15) and his associates for the study of enteric pressures in acute intestinal obstruction. To prevent injury to the loop of intestine it is enclosed in a bipedicle tube of skin which is mobilized from the skin of the abdomen exactly as in the preparation of a pedicle tube graft in plastic surgery. The preparation was found to have certain disadvantages. Thus it is necessary to exclude bones from the diet in order to avoid the danger of incarceration of a bone fragment in the loop with subsequent obstruction. Similarly, obstruction was noted in a long-haired animal from incarceration of a hair ball. Finally in the immediate postoperative period, there is a definite risk of the animal traumatizing the loop. This was en-

countered twice and was the cause of the only operative deaths in the series. When the skin around the loop is well healed, the animals do not appear to object to its presence and can be maintained in a healthy condition for many months.

These disadvantages appeared to be outweighed for the present purpose by the advantages, which include the fact that the loop is physiologically active, that there is no breach in the myenteric plexus, that the mesenteric blood and nerve supply is intact and finally that prolonged day-to-day observations of intestinal activity can be carried out without detriment to the animal.

For obvious reasons, all the loops used in the present study were prepared as far as possible at the same distance from the ileocecal valve, namely 25 cm. The average length of the loops studied was about 15 cm.

The method of recording the activity of these loops was a simple double tambour air-displacement system and proved, on the whole, to be fairly satisfactory. The excursions on the tracing do not give a linear representation of the activity in the loop since the displacement requires progressively more energy as the tension in the system increases, but the same criticism may be applied to almost any displacement system which has been used to record intestinal activity and since the same system is used throughout each experiment the results, though not strictly quantitative, are relatively valid for that experiment.

The animals were trained to lie on the observation table for three-hour periods and to eat their food on the table during the taking of a tracing.

PROCEDURE OF EXPERIMENTS

The following standard procedure was adopted after preliminary observations. The animal was fasted for forty-eight hours, water being allowed. It was then placed on the observation table and a control tracing taken. A standard meal was then given consisting of 350 gm. of fresh meat and 150 gm. of cracker meal. In the case of animals with gastric fistulas, 200 cc. of a milk and syrup mixture were given by gravity into the gastrostomy tube. The tracing was thereafter continued for one hour.

A second tracing was taken twenty-four hours after the meal and a third, the control tracing mentioned before, forty-eight hours afterward. The animal was thereupon fed again. It was thus possible to follow the activity of the ileum from one feeding to the next throughout a complete cycle. Of course, the tracings from day to day are not by any means entirely comparable because of the variations in the application of the recording device but the differences in activity were so striking and constant in the present study and were so easily confirmed by inspection and palpation of the loop that it was felt that, for the present purpose, the method was adequate.

RESULTS

Observations were carried out in normal* animals, vagotomized animals, animals with gastric fistulas, animals in which the food residues were shortcircuited

*The word "normal" is applied in this paper to animals for which an exteriorized loop of ileum in continuity had been established, as described in the section on methods, but which had not been submitted to any other operative procedure.

past the loop, and finally in animals with isolated loops (Fig. 1).

Normal animals. Using the standard technic mentioned in the preceding section, it was apparent that the activity in the loop bore a relationship to the ingestion of food. After the forty-eight hour fast, the loop was as a rule quiescent. Very few movements of any type were observed. Occasionally a period of ac-

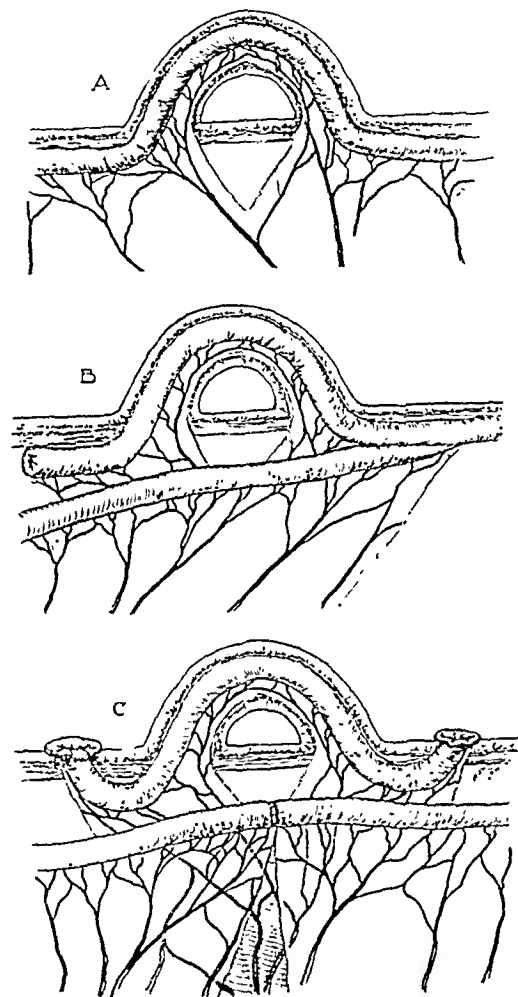


Fig. 1. Types of intestinal loops. A. Loop of ileum in continuity with nerve and blood supply intact, enclosed in bipedicle tube of skin; B, loop short-circuited, extrinsic nerve and blood supply intact; C, loop isolated, analogous to Thiry-Vella loop, extrinsic nerve and blood supply intact.

tivity of one or two minutes was observed but the periods of quiescence were prolonged and occupied by far the majority of the tracing. What movements were observed were feeble and as a rule consisted of a gentle type of segmentation, often rhythmic. Peristaltic waves were exceedingly uncommon after a forty-eight hour fast. Palpation of the loop showed it to be empty and flaccid. Although after a forty-eight hour fast the animal was, of course, hungry,

TABLE I

Normal dog. Time from feeding to motor response in lower part of the ileum

Dog	Average Time, Minutes	Variation, Minutes	Number of Experiments
1	2.5	1-7	10
2	3.6	2-5.5	10
3	2.5	1-6	11
4	2.2	1-4.5	8
5	4	1-6.5	8
6	3	1-7.5	6
Total number of experiments			53
Average time of response			3 minutes
Period of observation			6 months

nothing comparable to the violent hunger contractions described in the stomach was ever seen.

Feeding the standard meal resulted in a striking change. The loop, which had been quiescent and toneless, rapidly became extremely active with a considerable rise in tonus (Fig. 2). The average time from the beginning of the meal to the motor response in the loop in fifty-three experiments in six animals was 3.2 minutes, the range from one to seven and a half minutes (Table I). In one experiment the response was delayed for sixteen minutes but this was so different from the average response that it was discarded in the computation. After the motor response had occurred, the loop either remained active for the duration of the experiment or became quiescent again after a period of several minutes. In the latter case a second motor effect occurred after a few minutes. Thereafter movements were active to the end of the hour's tracing. The types of movement seen after feeding were most commonly propulsive forms of segmentation and peristaltic and tonus waves. The rhythmic contractions were not commonly seen.

The tracing taken twenty-four hours after feeding differed from that taken immediately after, mainly in two respects. First, periods of quiescence were common and second, true rhythmic contractions were quite frequently seen. Though this was true for the majority of tracings it was not true for all. Sometimes the tracing taken twenty-four hours after feed-

TABLE II

Time from feeding to motor response in lower part of ileum of dog before and after bilateral thoracic vagotomy

Period of Observation	Dog	Average Time, Minutes	Variation, Minutes	Number of Experiments
Before operation	1	2.9	1-7	10
	2	3.6	2-5.5	10
After operation	1	2	1-3	7
	2	2.1	1.5-2.5	7
Total number of experiments				34
Average time of response before vagotomy				3.2 minutes
Average time of response after vagotomy				2 minutes

ing was indistinguishable from that taken immediately after, both as to the occurrence and as to the type of activity, and again sometimes it resembled the tracing taken forty-eight hours after feeding, showing very long periods of quiescence. It must be realized that the hour's tracing represented only one hour out of twenty-four hours, and therefore variations were to be expected. Some observations were made on the effect of feeding after a twenty-four hour fast. The results were inconstant. If the loop were active before feeding, subsequent feeding did not then result as a rule in any increase in activity. If the loop were quiescent, a response was as a rule noted.

The vagotomized animal. Considering that the loop of ileum under observation was from 120 to 190 cm. from the pylorus and considering the time relationship of the response to feeding, it appeared likely that the motor effect was mediated reflexly through the motor nerves of the intestine. Accordingly double thoracic vagotomy was performed in two animals. One centimeter of each nerve was resected immediately above the esophageal hiatus in the diaphragm. The health of the animals appeared to be unaffected by the vagotomy.

The experiments were then repeated in the vagotomized animals (Table II). The results were somewhat unexpected since it was found that the motor response to feeding occurred as constantly and with similar time relationships in the vagotomized animals as in the normal animals (Fig. 2).

Animals with gastric fistulas. The fact that section of the vagi did not affect the occurrence of the motor

response to feeding appeared to indicate that the response was probably not a psychic feeding reflex mediated by the extrinsic nerves. Accordingly in two dogs, experiments were carried out on feeding by the gastric fistula. It was found that one precaution must be taken in this preparation. The food must be run into the stomach through the gastrostomy tube by gravity. If the food is forced into the stomach by a syringe, vomiting frequently occurs and the experiment is vitiated. The results of these experiments were as constant as those seen in the normal animals (Table III). The introduction of the food into the stomach of the animal was followed by a motor response in the loop of ileum in eleven experiments in two animals. Again the time relationships of the response were comparable to those in the normal animal.

Animals in which food residues were diverted past the loop. Since the motor response was not abolished by vagal section nor by gastric fistula feeding, attention was turned to the fact that the loop of ileum under consideration was in continuity with the rest of the small intestine. The contents of the intestine were therefore diverted past the loop by the following operation. The segment of bowel immediately oral to the exteriorized loop was sectioned. The upper end was then anastomosed to the ileum caudad to the loop, immediately above the ileocecal junction. The lower end was inverted and left in the abdomen as a cul-de-sac (Fig. 1B). Two things are to be noted about this preparation. First, the secretions from the mucosa in the loop empty into the ileum immediately above the

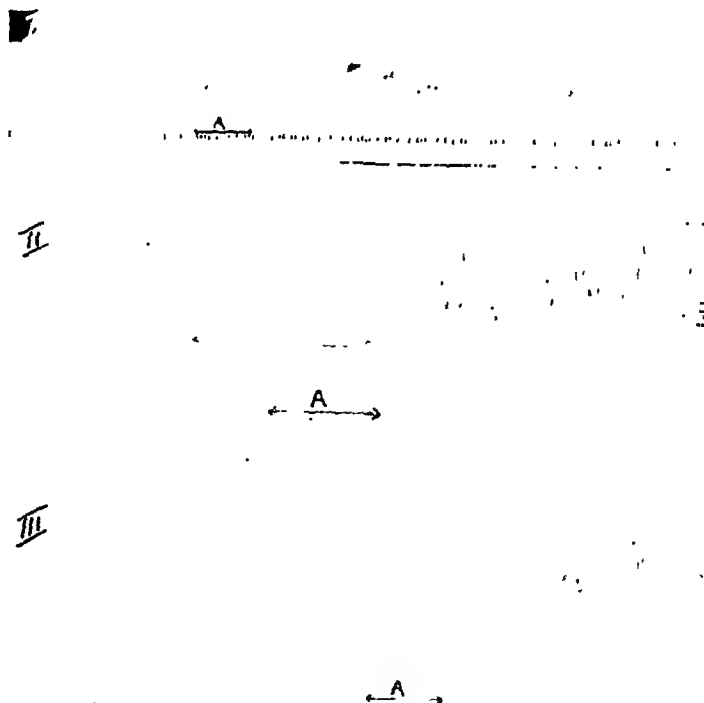


Fig. 2. Motor response to feeding in loop of ileum in continuity 25 cm. from ileocecal valve. I, normal animal; II, vagotomized animal; III, animal fed by gastric fistula. Animal fed at A. Time in five-second intervals.

TABLE III

Time from feeding to motor response in lower part of ileum of dog before and after gastrectomy

Period of Observation	Dog	Average Time, Minutes	Variation, Minutes	Number of Experiments
Before operation	5	4	1-5.5	8
	6	3	1-7.5	6
After operation*	5	2.1	1.5-3	3
	6	2.7	1-3	8
Total number of experiments				25
Average time before gastrectomy				3.6 minutes
Average time after gastrectomy				2.5 minutes

*Animal fed through gastric fistula.

cecum and second, the intrinsic plexuses and muscle layers in the loop are in continuity with the terminal part of the ileum at the caudad end of the loop. Since the direction of peristalsis in the small bowel is thought to be always caudad, it was thought that the regurgitation of food residues from the rest of the small intestine into the loop was unlikely, and that, as in the case of the Mann-Bollman fistula, the loop would be relatively free of food residues.

The experiments were repeated in this preparation. In contradistinction to the loops in continuity, this preparation showed very little correlation of activity in response to feeding. The activity in the loop was on the whole feeble. The regular chain of events seen in the normal animal, namely, the rapid response to feeding, followed by prolonged activity, gradually diminishing to quiescence at the end of forty-eight hours' fasting, was not commonly seen. As a rule the activity in the loop was unrelated to the ingestion of food and was no greater in the recently fed than in the fasting animal.

However, in eight experiments out of twenty-five a definite motor response to feeding was noted and, interestingly enough, the response had the same time relationships as in the normal animal (Table IV).

Animals with completely isolated loops. The inconsistent results in the preparation just described led

TABLE IV

Time from feeding to motor response in lower part of ileum of dog before and after short-circuit of exteriorized loop

Period of Observation	Dog	Average Time, Minutes	Variation, Minutes	Number of Experiments
Before operation	3	2.5	1-6	11
	4	2.2	1-4.5	8
After operation	3	No response		11
		3	1-5	5
	4	No response		6
		4	1.5-7	3
Total number of experiments				44
Before short-circuiting operation—constant, positive				
After short-circuiting operation—17 negative, 8 positive				

one to observe the effect on the completely isolated loop. This was done by sectioning both ends of the exteriorized loop within the abdomen, restoring the continuity of the bowel and bringing out both ends of the exteriorized loop through a stab wound in the abdominal wall. The preparation was now analogous to the Thiry-Vella fistula except that it was possible to record its activity without the introduction of a foreign body (Fig. 1C). In this preparation there was, of course, no possibility of food residues entering the loop, a condition which was only presumptive in the short-circuited loop.

While the short-circuited loop occasionally showed a correlation of activity and feeding, the completely isolated loop never did so (Table V).

In nineteen experiments on two animals the results were uniformly negative. The activity in the completely isolated loops was always feeble. Long periods of quiescence were noted and these were as common in the recently fed animal as in the fasting animal.

TABLE V

Time from feeding to motor response in lower part of ileum of dog before and after interruption of continuity and complete isolation of loop

Period of Observation	Dog	Average Time, Minutes	Variation, Minutes	Number of Experiments
Before operation	4	2.2	1-4.5	8
	5	4	1-6.5	8
After operation	4	No response	—	10
	5	No response	—	9
Total number of experiments				35
Before isolation of loop—constant, positive				
After isolation of loop—constant, negative				

The type of activity was predominantly segmentation, and true rhythmic segmentation was comparatively common. It is instructive to note the similarity of activity in the loop of ileum in continuity in the animal which has fasted for forty-eight hours and that in the isolated loop at all times. In both, quiescence is much more common than activity; in both, peristaltic waves are extremely uncommon; in both, segmentation of a feeble character is the commonest type of movement.

COMMENT

The great constancy of the motor response to feeding in the lower part of the ileum of the dog together with the relatively constant time relationship of the response bears out the findings of Cash (7), Macewen (8), Hertz (6), Short (9), Hinrichsen and Ivy (10) and Castleton (12). The fact that fasting is necessary to permit of constant results has been noted by Hinrichsen and Ivy.

That the response is not entirely a psychic one is borne out by two findings: first, that the mere presentation of the meal to the animal without permitting it to eat never resulted in a motor response in the ileum, and second, that the motor response was as constant after feeding by a gastric fistula as after

normal feeding. Neither of these findings, of course, entirely excludes a psychic response.

The unexpected finding that the response occurs as constantly after double thoracic vagotomy as before is further evidence of something which many gastro-intestinal physiologists, including Cannon (16) and Alvarez (17), have emphasized, namely the independence of the intrinsic enteric mechanism.

It is not, of course, positive evidence that, in the normal animal, the vagi do not play a part in mediating the motor response, but the great similarity of the response in the vagotomized and the normal animal both as to degree and as to time relationship is suggestive of some other mediation.

The findings after interruption of the continuity of the bowel, by short-circuiting or by complete isolation, appear to indicate that the mediation of the motor effect depends on the continuity of the intestine. Both the short-circuited loop and the isolated loop had, of course, the extrinsic nerve supply intact as in a Thiry-Yella fistula. If mediation were by way of the extrinsic nerves, one would have expected a motor response as constant in the isolated loop as in the loop in continuity. This was not the case. In seventeen experiments out of twenty-five in the short-circuited preparation in which the lower end only was in continuity no motor response to feeding occurred. In all nineteen experiments in the preparation in which the loop was isolated the result was negative. These findings would also tend to indicate that the motor response is not humoral in origin, and are in harmony with those of Puestow (11).

The findings with respect to fasting are, perhaps, not unexpected. It is reasonable that the degree of activity of an organ should be governed by the physiologic demands made on it. Thus fasting the normal animal for twenty-four hours resulted in a lesser degree of activity in the loop of ileum than that seen in the recently fed animal and fasting for forty-eight hours resulted in even less activity. It is not entirely clear why fasting for forty-eight hours should result in a greater diminution in activity than fasting for twenty-four hours since it is generally believed that

the small bowel has passed on all its food residues at the end of twenty-four hours. Whatever the explanation, the finding was constant, and perhaps is of interest to the surgeon who wishes to put an intestinal anastomosis at rest as far as possible.

Not only the degree of activity, but also the type of activity, was governed by the ingestion of food. Thus in the loop of ileum in the recently fed animal, peristaltic waves and tonus changes were common together with propulsive forms of segmentation. In the fasting animal, on the other hand, peristaltic waves were extremely uncommon and tonus changes were seldom seen. The commonest type of movement seen in the ileum of the fasting animal was gentle segmentation, often rhythmic in character.

SUMMARY

The activity of exteriorized loops of the lower part, of the ileum in continuity, enclosed in bipediced tubes, of skin, was studied in the dog in relation to the ingestion of food. A regular cycle of activity was noted, in the normal animal: namely, a rapid motor response to feeding, followed by prolonged activity which gradually diminished until, after forty-eight hours of fasting, the activity was extremely feeble.

The motor response was noted as constant after feeding by gastric fistula as in the normal animal. Similarly the motor response was as constant after double thoracic vagotomy as before.

Partial interruption of continuity by a short-circuiting operation resulted in inconstant results. Complete isolation of the loop resulted in absence of the motor response to feeding and complete dissociation of the activity of the loop from the ingestion of food.

The evidence is taken to indicate that the degree, and type of activity in the lower part of the ileum of the dog is intimately connected with the ingestion of food, that the so-called gastro-ileal reflex is not merely a feeding reflex, that it depends for its mediation on the continuity of the intestine, and finally that the vagus nerves, which are generally believed to be the motor nerves of the small intestines, play little part in the mediation.

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Over Two Thousand Estimations of the pH of Representative Foods*

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BOTH the medical profession and the laity have been besieged with a tremendous amount of inaccurate and irreconcilable information relative to the acidity of foods. Whenever reaction of foods is mentioned, there is confusion over metabolic end-products versus gastric and intestinal effects. The "reaction" of a food is frequently judged by the pH or titratable acidity of the urine subsequent to the ingestion of the food. This viewpoint is not entirely tenable even with reference to the metabolic behavior of foods (unpublished observations of Bridges and Mattice) and it certainly has no bearing upon the "reaction" of foods within the alimentary tract. Foods as eaten create a mental impression of neutrality or acidity. An extraordinarily acid-tasting food, however, may be altered in the body to a definitely alkaline substance. Neutral foods, on the other hand, may give rise to acids during the course of metabolism. The designation, therefore, of the reaction of a food requires qualification as to point of view.

Little or no information has been available on the true acidity (pH) of food as ingested. Bridges (1) presents a tabulation of less than three dozen items, most of which are fruits. He also cites Smith (2) as placing fresh egg-white at pH 7.97 with elevation to 9.2-9.5 on loss of CO₂ during storage. The quality was best preserved by holding this at 7.5-8.0 by means of carbon dioxide. Ulrik and Davidsen (3) record the pH of the new-laid egg at approximately 8.2 with a rapid rise to 9.4 during the first twelve hours succeeded by gradual increase to 9.8 by the ninth day. They found no distinct change thereafter until the 53rd day.

Quoting Clark (4) Bridges gives flour a pH of 5.7, bread 5.3, cake 6.7 and macaroni 5.9.

Clague and Fellers (5) used the quinhydrone electrode for the study of cider made from different varieties of apples; their values ranged from pH 3.1 to 4.0, including data with reference to clarification processes. Kidd and Hanes (6) reported increase in the pH value (2.8-3.7) during storage of apples, the rise being related to warmth of storage atmosphere.

Haas (7) examined different sections of the avocado for variations in pH. The inner and outer portions of the soft edible pulp (without skin) of the stem halves of mature fruit were pH 6.82 and 6.72 respectively whereas the corresponding portions of the tip halves had values of 6.64 and 6.44.

Coulter and co-workers (8) found blue or American Roquefort cheese to reach a maximum of pH 4.7 within 24 hours of manufacture. Except for temporary

increase in acidity following piercing, the acidity decreased gradually to a pH of approximately 6.5 at the end of the third month. Subsequently, the pH fell to about 5.7 by the end of the ninth month beyond which no experiments were conducted.

Pont and Sutton (9) detected no correlation between the pH of butter and the bacterial or yeast counts. The majority of their samples varied from 7.0 to 7.7. Kretchmar (10) found marked correlation between the initial flavor score and the pH values, the butters with higher flavor scores generally being less acid than those with lower scores. The optimum acidity for keeping quality of butter was stated to be pH 6.7-6.9, it being regarded as undesirable to store butter if the pH was less than 6.3 or more than 7.1.

Winton (11) cites Fiehe and Kordatzki (1928) as reporting pH 3.8-4.3 for pure honey and pH 3.0-4.0 for artificial honey.

Kugelmass (12) in a brief report offers a few values for the pH of fruit juices. Information on this and other laboratory data is exceedingly scant, neither the laboratory responsible for the analyses nor details as to technique being revealed. The unusual acidity of the orange juice (pH 3.0) sampled by Kugelmass is mentioned by Dimmler (13) who observed values from pH 3.63 to 3.99, which is in essential agreement with our data. Kugelmass states that a colorimetric procedure was used to ascertain the pH. This may account for the fact that his beet juice (pH 8.8) is at wide variance with our findings (pH 5.23-5.90 on 6 tests of fresh home-cooked beets and pH 5.32-5.56 on 12 tests of canned beets which had been chopped or strained for baby feeding). Kugelmass reports pH 4.3 for apple juice as against our results of pH 3.38-3.62 for canned juice, 3.09-3.40 for canned apple sauce, and 3.33-3.84 for eating apples.

Valaer (14) offers over one hundred pH values for different types of domestic and foreign brandy, the majority of which varied from pH 3 to 5, the acidity in part being attributed to slow production of sulphuric acid.

That other data exist cannot be questioned, but scattered values buried in investigational reports of various types are difficult to locate. The obvious paucity of easily accessible material prompted us to accumulate extensive data under standard and comparable conditions so that clinicians and nutritionists will have at their disposal fundamental information regarding the actual reaction of foods as ingested.

EXPERIMENTAL PROCEDURES

The taking of this lengthy series of pH measurements was facilitated by use of the Hellige pH meter which utilizes a glass electrode. Whenever readings were made, the instrument was first checked against

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0.05 molar acid potassium phthalate (pH 3.97) and the setting verified at the conclusion of each series. The meter functioned satisfactorily except for a brief period at the time six hundred tests had been completed. Sluggishness of response led to thorough testing of the batteries, connections, and glass electrode. Although it met all the requirements specified by the manufacturer, the bulb-type glass electrode was replaced by a new one of the spear type. Since no benefit was derived from this change, new batteries were introduced with separate checking after each insertion. Despite the fact that the used batteries had been declared by a competent electrician to be perfectly satisfactory and despite the fact that the expected life of the batteries had not been exceeded, the instrument recovered full sensitivity immediately on being fitted with a new set of batteries. The bulb-type electrode was again employed since it proved to be the more suitable for our purpose. At the conclusion of these experiments, the batteries again required replacing. The glass electrode, however, still met every demand made of it.

Separation of two solutions by a suitable glass membrane results in almost instantaneous development of a stable potential which depends upon the hydrogen-ion concentration of the solutions. Utilization of fixed reference cells together with means of maintaining the electrical circuit enable the pH meter to provide quick and accurate pH measurements in almost any solution regardless of suspended matter, color, viscosity, the presence of oxidizing or reducing agents, etc. The glass electrode is particularly well adapted for obtaining pH data on foods. The procedure is extremely simple, requiring only immersion of the inverted tip of the calomel cell and the glass membrane in the test sample together with a little intelligent manipulation of the instrument.

The pH meter was operated by two persons only. Sensitivity was maintained by regular over-hauling for tightness of electrical connections. The instrument was used under semi-shielded conditions in rooms known to be free of electrical disturbances. Except where specified, test samples were allowed to reach room temperature before being measured. The instrument was adjusted to this temperature (20-28° C., usually 25°) which was kept fairly constant. Lack of temperature control may be responsible for appreciable error. Although the smallest scale division on the meter dial is 0.1 pH unit and the precision about one-half of this, observations have been reported as read.

Correct procedures for washing the electrodes between tests were ascertained experimentally. This was a time-consuming process because of the nature of the samples. Repeated dousing with distilled water or a forced stream usually dislodged the food particles. Fresh saturated KCl was used generously to keep the inverted tip of the calomel half-cell free from contaminants, including the rinse water. Filter paper was employed to absorb adhering drops of water. When necessary, "pencils" of moist filter paper were applied to the glass membrane to remove sticky samples.

The nature of the food determined the method of preparation necessary for testing. As a rule, the fruits could be mashed with a spoon or fork. The vegetables often required passage through a chopper for release

of the juices. Dry cereal products, such as bread, were moistened with a minimum amount of water. Satisfactory results, however, could be obtained without having the food obviously wet. Although glass cells were at first used to hold the test items, paper ramekins were later employed on suitable items to avoid an excessive amount of washing.

Since the work extended over many months, it was feasible to examine a reasonably complete list of foods at the most advantageous season and also, wherever practical, to test the separate items over a period of time thus avoiding constancy of results due solely to method of sampling. An effort was made to test the various foods six times so as to provide some indication of variability.

OBSERVATIONS

The results of the investigation are presented in four tables. Reciped foods and soda-fountain items have been separated from the main table and grouped in Table III. By reciped foods it is to be understood that standard recipes have been used for preparation. Canned items (commercial) are included in Table I since they are not subject to the wide variation anticipated under changing kitchen conditions. Table II demonstrates the rise in pH associated with dilution of a few common fruit juices. Changes in the pH of eggs with age are shown in Table IV.

Hydrogen-ion Concentration versus pH. The reaction of the various foods tested is presented in terms of pH. It will be noted that values designated as "average pH" are not given. Inasmuch as pH is logarithmic, it is not permissible to obtain its arithmetic mean. pH values cannot be treated as though they were actual numbers. No serious error, perhaps, would be committed in averaging the tabulated results of the foods herein presented, but such a practice would reveal lack of comprehension of the fundamental meaning of the term pH.

Since many workers in the field of nutrition have had limited experience with this term now current in every discussion, it is desirable to demonstrate by what simple means the significance of pH can be comprehended. The acidity of a medium is dependent upon the number of hydrogen-ions present. When expressed in the conventional forms for designating concentration, the smallness of the value makes representation awkward. For example, a tangerine may be known to contain 0.00001467 gram H⁺ per liter. Because of the difficulty in handling such a number, it is customary to write it as 4.467×10^{-5} . This arithmetical value may be more conveniently used in its logarithmic form, $1 \times 10^{-4.35}$, but this renders it well-nigh incomprehensible to the average interested reader. Once cast in this form, the corresponding pH may be obtained by discarding everything but the 4.35. This appears to be a number which can be easily understood, but in reality it is not a number at all. The four designates only the position of the decimal point in the real number to which the pH corresponds. Although the 35 is logarithmic, it cannot be located in any "log" table since it is negative. After conversion to a positive value, the table will reveal the significant figures in the real number, the decimal point being inserted as already indicated.

Moving acid on the pH scale from the theoretical neutral point of 7, each interval (as 0.1 pH) is greater

TABLE I
pH of representative foods*

Item	pH					Item	pH				
All Bran	6.00	6.50	5.62	6.63	6.70	5.19	Caviar, American				5.40
Artichokes, stuffed with capers, in olive oil						6.58	Celery	6.88	6.00	6.86	6.70
Apples, eating	3.33	3.35	3.58	3.36	3.84	3.84	Celery, cooked	5.37	6.35	6.50	6.50
Apples, baked with sugar	3.20	3.22	3.28	3.55	3.54	3.50	Celery, Cabbage	5.92	6.02	6.22	6.26
Apple Juice, canned	3.52	3.62	3.38	3.40	3.35	3.42	Celery Knob (Celericac), cooked	6.80	6.71	6.65	6.71
Apple Sauce, canned	3.40	3.23	3.15	3.10	3.09	3.12	Cereal, strained, Clapp	6.30	6.44	6.44	6.44
Apple Sauce, chopped, Clapp	3.24	3.24	3.24	3.24	3.35	3.35	Chayote, cooked	6.30	6.05	6.00	6.13
Apple Sauce, strained, Clapp	3.24	3.24	3.24	3.24	3.42	3.42	Cheese, American, mild, Kraft				4.90
Apple-currant Jelly, com.						3.00	Cheese, Camembert				7.44
Apricots	4.50	4.22	4.67	4.33	4.62	4.18	Cheese, Cheddar, English				6.00
Apricots, canned	3.46	3.42	3.42	3.15	3.42	3.47	Cheese, Cottage				6.02
Apricots, unsweetened, canned						3.78	Cheese, Cream, Philadelphia	4.70	4.10	4.45	4.88
Apricots, puréed, Stokely	3.80	3.83	3.70	3.68	3.62	3.42	Cheese, Edam				6.40
Apricots, strained, Clapp	3.81	3.78	3.81	3.72	3.95	3.72	Cheese, Old English, Kraft				6.15
Apricots, dried, stewed	3.51	3.37	3.50	3.40	3.40	3.30	Cheese, Roquefort	5.41	5.64	5.98	6.02
Apricot Nectar (pulp, juice, sugar, water), com.						3.75	Cheese, Snappy, Kraft				5.18
Arrowroot Crackers						6.63	Cheese, Stilton				5.70
Arrowroot Gruel						6.37	Cheese, Swiss Gruyere				6.62
Artichokes, French, cooked	6.00	6.75	6.70	6.81	6.67	6.87	Cherries, California	4.64	4.16	4.16	4.06
Artichokes, Jerusalem, cooked	6.00	6.93	6.00	6.00	5.98	6.93	Cherries, frozen	3.37	3.36	3.32	3.35
Asparagus, cooked	6.03	6.13	6.10	6.16	6.10	6.10	Cherries, black, canned	3.80	3.93	3.86	3.87
Asparagus, frozen, cooked	6.42	6.35	6.39	6.48	6.40	6.43	Cherries, Maraschino, com.	3.62	3.60	3.50	3.49
Asparagus, green, canned	6.21	5.32	5.23	6.30	6.20	6.30	Cherries, red, water-pnck	3.29	3.29	3.25	3.32
Asparagus, strained, Clapp	5.99	6.09	6.09	4.52	6.09	4.80	Cherries, Royal Anne, com.	3.80	3.80	3.82	3.83
Avocado, Cuban	6.47	6.24	6.42	6.27	6.58	6.64	Chicken, broiled	6.60	6.26	6.25	6.13
Baby Soup, unstrained, Clapp	6.00	6.00	6.00	6.00	6.00	6.00	Chicken, also see Fowl				
Bacon, broiled	5.80	5.20	5.89	6.12	6.10	6.00	Chicken Liver, broiled				5.99
Bacon, Canadian, broiled	6.70	6.60	6.45	6.57	6.50	6.73	Chicory	6.90	6.05	6.05	5.89
Bananas, red	4.58	4.62	4.62	4.65	4.68	4.76	Chives	5.64	5.75	5.25	6.10
Bananas, yellow	5.21	5.29	5.00	5.12	5.04	6.10	Clams	6.40	6.68	6.60	7.02
Barley, cooked	5.19	6.25	6.32	6.28	6.32	5.29	Cocanut, fresh	6.90	6.00	6.00	6.62
Bass, sea, broiled	6.70	6.70	6.64	6.70	6.58	6.68	Codfish, boiled				6.32
Beef, striped, broiled	6.60	6.50	6.60	6.68	6.60	6.70	Conebs	7.52	8.20	8.40	8.05
Beans, black, cooked	6.82	6.78	5.93	6.00	5.98	6.02	Corn, Golden Bantam, cooked on cob	6.76	7.04	6.35	6.81
Beans, Boston-style, home-baked	5.05	5.09	6.12	6.15	6.12	6.12	Corn, frozen, cooked	7.33	7.44	7.50	7.57
Beans, Boston-style, com.						5.42	Corn, canned	6.09	6.41	6.67	6.97
Beans, pork and tomato sauce, canned						5.51	Corn Flakes	6.38	6.00	4.88	4.90
Beans, vegetarian, tomato sauce, canned						5.32	Corned Beef, brisket, boiled				6.13
Beans, kidney cooked	6.85	6.90	5.00	6.01	6.02	6.07	Corned Beef, pressed, canned	5.75	5.70	6.85	5.96
Beans, lima, green, cooked	6.19	6.21	6.30	6.19	6.28	6.40	Cranapple Jelly, com.				3.02
Beans, lima frozen, cooked	6.50	6.56	5.75	6.67	6.45	6.90	Cranberry, cooked	6.62	6.77	6.92	6.97
Beans, lima, canned	5.76	6.78	5.86	6.90	6.86	6.90	Cranberry Juice, canned	2.40	2.52	2.35	2.31
Beans, lima, dried, cooked	6.12	6.40	6.37	6.40	6.48		Cranberry Sauce, com.				2.40
Beans, navy cooked	5.96	6.00	6.01	6.01	6.10		Cream, 20 per cent	5.52	6.62	6.68	5.52
Beans, string, cooked	5.73	6.73	6.86	6.08	6.20	6.10	Cream, 40 per cent	6.44	6.60	6.60	6.62
Beans, string, canned						4.72	Cream of Wheat, cooked	6.06	6.10	6.16	6.16
Beans, string, chopped, Clapp	5.01	5.01	5.01	5.01	5.01	5.01	Cucumbers	5.70	6.78	6.18	6.52
Beans, string, puréed, Stokely	4.66	4.96	6.00	4.80	4.84	4.78	Cucumbers, pickled				3.70
Beans, string, strained, Clapp	5.08	6.08	5.08	5.08	5.12	5.15	Cucumbers, pickled, bread-and-				3.68
Beans, wax, cooked	6.62	6.60	6.58	5.61	6.70	6.68	butter type				3.68
Beef Broth, Clapp	6.14	6.18	6.14	6.20	6.20	6.20	Dates, Dromedary	4.58	4.74	4.81	4.88
Beef with Vegetables, chopped, Clapp	5.50	5.60	6.19	6.00	5.88	5.60	Duck, roasted	6.62	5.40	7.02	5.28
Beef with Vegetables, strained, Clapp	6.17	5.17	5.18	5.18	5.05	5.16	Eggs, new-laid, whole				6.08
Beef, Filet Mignon, broiled						6.40	white				7.36
Beef, pot-roasted						6.88	yolk				6.10
Beef, ribs roasted						6.22	Eggs, also see Table IV				
Beef, round, chopped, broiled						6.23	Eggplant, cooked	6.41	5.31	6.40	6.45
Beef, scraped raw						5.60	Escarole	6.70	6.02	5.92	6.00
Beef-steak, sirloin, broiled						5.61	Farina (1 lb. cooked ½ hour)	6.98	5.98	5.80	6.82
Beef greens, cooked	6.62	6.58	7.01	6.70	6.70	6.77	Fennel (Anise)	6.48	6.62	6.72	5.73
Beets, cooked	5.23	5.52	6.72	5.41	5.52	5.15	Fennel, cooked	6.02	6.00	6.00	5.88
Beets, canned	4.95	4.97	4.98	4.97	4.97	4.92	Figs, Calamyrna	5.05	6.08	5.08	5.18
Beets, chopped, Clapp	5.56	5.56	5.56	5.56	5.32	5.32	Figs, canned	6.00	6.00	4.92	5.00
Beets, strained, Clapp	5.66	5.56	5.56	5.56	5.32	5.38	Flounder, broiled	6.28	6.55	6.43	6.40
Bouillon, com.						4.90	Flounder, fillet, broiled	6.90	6.73	6.60	6.57
Blackberries, Washington	4.40	4.60	4.40	4.40	4.25	5.15	Fowl, boiled	6.20	6.10	6.70	6.40
Blueberries, Maine	3.22	3.32	3.12	3.22	3.18	3.20	Frankfurters, boiled	6.10	6.18	6.15	6.18
Blueberries frozen	3.35	3.17	3.11	3.16	3.20	3.22	French Dressing, Kraft				3.52
Bluefish (Boston), fillet, broiled	6.50	6.30	6.10	6.13	6.09	6.06	Fruit, mixed, dried, stewed (apricots, prunes, peaches, apples)	3.53	3.59	3.60	3.27
Bran Flakes	6.45	5.15	6.60	5.67	5.50	5.65	Gelatin, plain jelly				3.33
Bread, Boston brown						6.53	Gelatin Dessert:				2.60
Bread, corn						6.17	Lime				3.19
Bread, cracked wheat						6.43	Raspberry				3.37
Bread, pumpernickel						4.10	Sherry-wine				3.19
Bread, rye	5.46	5.50	5.48	5.20	6.60	5.63	Goose, roasted	5.96	6.90	5.98	5.00
Bread, white	5.42	5.50	5.67	5.29	6.43	5.36	Graham Crackers	7.12	7.10	7.10	7.10
Bread, whole wheat	6.60	6.48	5.85	5.60	6.47	5.61	Grapes, Concord	2.79	3.00	2.95	2.91
Breadfruit, cooked						5.33	Grapes, Lady Finger	3.65	3.58	3.53	3.53
Broccoli, cooked	6.11	6.16	6.52	6.32	6.40	6.30	Grapes, Malaga	3.70	3.71	3.78	3.71
Broccoli, frozen, cooked	6.20	6.88	6.43	6.50	6.43	6.48	Grapes, Niagara	2.80	2.52	3.14	3.10
Brunfels Sprouts, cooked	6.05	6.15	6.00	6.01	6.05	6.01	Grapes, Ribier	3.73	3.50	3.77	3.75
Buttermilk	4.48	4.42	4.45	4.41	4.83	4.42	Grapes, Seedless	3.81	2.90	3.12	3.28
Cabbage, green	5.90	6.13	6.18	5.90	5.79	6.29	Grapes, Tokay	3.72	3.50	3.69	3.61
Cabbage, green, cooked	6.77	6.82	6.70	6.65	6.38	6.56	Grapefruit	3.70	3.42	3.75	3.22
Cabbage, red	5.47	5.52	5.86	6.00	5.75	5.82	Grapefruit, canned	3.10	3.08	3.29	3.32
Cabbage, red, cooked	6.31	6.31	6.42	6.31	6.21	6.41	Grapefruit Juice, canned	3.25	3.18	3.00	2.90
Calves' Liver, broiled						6.45	Grapenuts	5.40	5.22	5.18	6.20
Cantaloupe	6.57	6.28	6.43	6.17	6.68	7.13	Greens, Mixed, chopped, Clapp	6.22	5.22	6.22	6.22
Carrots	6.00	5.88	6.98	5.99	5.96	6.00	Greens, Mixed, strained, Clapp	6.30	6.30	6.30	6.30
Carrots, cooked	5.70	6.80	5.88	5.62	6.54	5.58	Grenadine Syrup, Giroux				2.51
Carrots, canned	5.20	5.22	5.20	5.18	5.19	5.20	Guava Jelly, com.				2.73
Carrots, chopped, Clapp	5.56	5.56	5.56	5.56	5.30	6.30	Guavas, canned				3.70
Carrots, puréed, Stokely	4.55	4.75	5.00	4.72	4.74	4.67	Haddock, fillet, broiled	6.48	6.21	6.17	6.82
Carrots, strained, Clapp	5.10	5.10	5.10	5.10	5.10	5.10	Ham, fresh, baked				5.90
Cauliflower, cooked	6.45	6.48	6.67	6.72	6.71	6.80	Ham, smoked, baked				6.80
Cauliflower, frozen, cooked	6.07	6.02	6.10	5.90	6.95	6.00	Ham, smoked, boiled				6.23
							Hamburgher, broiled				6.22
							Hominy Grits, cooked	5.99	6.00	6.02	6.20
							Honey	3.70	3.90	3.78	3.78
							Horsradish, freshly ground				5.35
							Horsradish, prepared, com.				3.66
							Horleberries, cooked with sugar				3.38
							Junket-type Dessert:				6.27
							Raspberry				6.49
							Vanilla				

*Data is presented for the edible portion of foods in the raw state unless otherwise designated. Cooking signifies boiling unless otherwise specified. The general order is as follows: raw, home-cooked, frozen, canned, commercial (com.), dried, etc. Trade names are italicized.

TABLE I (CONTINUED)

Item	pH						Item	pH					
Kale, cooked	6.70, 6.77, 6.80, 6.38, 6.38, 6.40						Plums, spiced, com.						3.64
Karo syrup						4.50	Plum Nectar (pulp, juice, sugar, water), com.						3.45
Ketchup, com.					3.89, 3.92		Pollack, filet, broiled					6.72, 6.82	
Kippered Herring, Marshall	6.10, 5.87, 6.10, 6.17, 6.14, 6.17						Pomegranate	3.00, 3.10, 3.03, 2.98,	2.93, 2.96				
Kohlrabi, cooked	5.72, 5.72, 5.72, 5.82, 5.82, 5.78						Porgy, broiled	6.47, 6.43, 6.49, 6.43,	6.40, 6.40				
Kumquats, Florida	3.70, 4.25, 3.80, 3.64, 4.03, 3.68						Pork Chop, broiled					6.53, 5.99	
Lamb Chops (rib), broiled	5.25, 6.57, 6.00, 5.55, 6.00						Pork Tenderloin, fresh, baked					6.83, 6.42	
Lamb Kidneys, broiled					6.51, 6.30		Potatoes, see Table III						
Lamb, rack, roasted						6.55	Prunes, dried, stewed	3.84, 3.92, 3.72, 3.72,	3.76, 3.69				
Lamb with Vegetables, chopped, Clapp	5.98, 6.01, 6.01, 6.01, 5.90, 5.90						Prunes, chopped, Clapp	3.68, 3.68, 3.65, 3.64,	3.75, 3.75				
Leeks	5.77, 5.97, 5.51, 6.07, 5.72, 5.62						Prunes, puréed, Stokely	3.82, 3.83, 4.00, 3.63,	3.60, 3.60				
Leeks, cooked	6.12, 5.79, 6.05, 6.05, 6.05, 6.16						Prunes, strained, Clapp	3.68, 3.83, 3.68, 3.68,	3.75, 3.75				
Lemon Juice	2.05, 2.05, 1.98, 2.10, 2.05, 2.05						Prune Juice, home-made	3.97, 3.96, 3.97, 3.95,	3.95, 3.97				
Lemon Juice, canned						2.32	Prune Juice, com.					3.78	
Lentils, cooked	6.83, 6.32, 6.36, 6.32, 6.35, 6.32						Puffed Rice	6.27, 6.40, 6.27, 6.34,	6.34, 6.20				
Lettuce, Boston	6.05, 6.09, 5.89, 5.98, 6.00, 5.92						Puffed Wheat	5.61, 5.58, 5.77, 5.70,	5.32, 5.26				
Lettuce, Iceberg	6.00, 5.70, 5.70, 6.06, 6.13, 6.00						Quince, fresh, stewed	3.37, 3.12, 3.16, 3.20,	3.20, 3.22				
Lime Juice	2.10, 2.00, 2.00, 2.11, 2.15, 2.25						Quince Jelly, com.					3.70	
Liver Soup, Clapp	5.60, 5.60, 5.60, 5.60, 5.58, 5.59						Radishes, red	5.85, 5.90, 6.05, 5.98,	6.04, 6.03				
Liver with Vegetables, Clapp	5.29, 5.31, 5.31, 5.31, 5.35, 5.35						Radishes, white	5.58, 5.61, 5.69, 5.57,	5.52, 5.52				
Liverwurst	5.40, 5.60, 5.72, 5.75, 5.72, 5.82						Raisins, seedless					4.10, 3.80	
Lobster, cooked	7.26, 7.30, 7.17, 7.43, 7.28, 7.10						Ralston (1:8, cooked ½ hour)	6.19, 6.21, 6.24, 6.35,	6.30, 6.19				
Macaroni, boiled	6.39, 6.41, 5.60, 6.00, 5.10, 6.00						Raspberries, California	3.70, 3.88, 3.91, 3.62,	3.93, 3.95				
Maekel, King, broiled	6.50, 6.43, 6.47, 6.26, 6.33, 6.37						Raspberries, New Jersey	3.72, 3.50, 3.50, 3.74,	3.82, 3.60				
Maekel, Spanish, broiled	6.36, 6.07, 6.14, 6.22, 6.10, 6.25						Raspberries, frozen	3.22, 3.18, 3.21, 3.20,	3.26, 3.22				
Maltex (1:8, cooked ½ hour)	5.81, 5.85, 5.89, 5.90, 5.86, 5.90						Raspberry Jam, com.	2.87, 3.06, 3.07, 3.10,	3.17, 3.08				
Mangoes, Florida	3.40, 4.43, 3.97, 4.41, 4.63, 4.17						Red Pepper Relish, com.					3.62, 3.10	
Maple Syrup						5.15	Rhubarb, California, stewed	3.27, 3.34, 3.26, 3.24,	3.27, 3.20				
Matzos						5.70	Rice, brown, cooked	6.25, 6.42, 6.47, 6.60,	6.70, 6.83				
Melba Toast						5.08, 5.30	Rice, white, cooked	6.50, 6.68, 6.15, 6.20,	6.00, 6.38				
Melons, Casaba	5.90, 5.78, 5.57, 5.62, 5.58, 6.00						Rice, wild, cooked	6.08, 6.23, 6.30, 6.33,	6.47, 6.33				
Melons, Honey Dew	6.43, 6.00, 6.42, 6.67, 6.28, 6.50						Rice Krispies	5.70, 5.73, 5.42, 5.60,	5.40, 5.41				
Melons, Persimn	6.30, 6.23, 6.09, 5.90, 6.29, 6.38						Rolls, white		5.52, 5.52, 5.46				
Milk, Grade A (N. Y.)						6.68, 6.68, 6.68	Romaine	5.90, 5.78, 5.98, 5.92,	6.06, 6.06				
Milk, Grade B (N. Y.)	6.62, 6.69, 6.70, 6.77, 6.68, 6.25						Salmon, fresh, boiled					6.85	
Milk, Acidophilus	4.13, 4.25, 4.15, 4.15, 4.09, 4.09						Salmon, fresh, broiled					6.38, 6.38	
Milk, condensed						6.33	Salmon, Red Alaska, canned	6.17, 6.07, 6.07, 6.10,	6.16, 6.16				
Milk, evaporated	6.01, 6.10, 6.11, 6.13, 6.11, 5.98						Sardines, Portuguese, in olive oil	5.72, 5.42, 5.77, 5.79,	5.93, 5.90				
*Milk, peptonized						7.10	Saltines	6.89, 6.05, 6.00, 6.80,	6.70, 6.10				
Milk, Goat's						6.48	Sauerkraut, cooked	3.50, 3.45, 3.46, 3.45,	3.47, 3.47				
Mint Jelly, com.						3.01	Sausage, pan-broiled					6.74, 6.50	
Molasses	5.63, 4.67, 5.20, 5.27, 5.32, 5.32						Scotch Broth, com.					5.92	
Mushrooms, cooked	6.21, 6.20, 6.17, 6.18, 6.18, 6.22						Shad Roe, sautéed	5.90, 5.90, 5.87, 5.87,	5.70, 5.83				
Mushroom Soup, Cream of, canned						5.95	Shallots, cooked	5.60, 5.70, 5.62, 5.60,	5.53, 5.60				
Mussels	6.20, 6.35, 6.58, 6.85, 6.85, 6.60						Sherbet, raspberry, com.					3.69	
Mustard, prepared, com.						3.55	Shredded Ralston	5.50, 5.49, 5.50, 5.53,	5.32, 5.60				
Nectarines	4.18, 3.94, 3.92, 3.97, 3.92, 4.06						Shredded Wheat	6.05, 6.05, 6.38, 6.20,	6.18, 6.49				
Noodles, boiled	6.21, 6.30, 6.08, 6.08, 6.30, 6.50						Shrimp, boiled	7.39, 7.40, 7.19, 7.41,	7.79, 7.45				
Oatmeal (1:8, cooked ½ hour)	6.30, 6.29, 6.28, 6.20, 6.20, 6.60						Smelts, sautéed	6.67, 6.76, 6.87, 6.90,	6.76, 6.86				
Okra, cooked	6.42, 6.57, 6.42, 6.57, 6.62, 6.31						Soda Crackers	6.83, 5.65, 6.40, 7.08,	7.32, 7.08				
Olives, green						3.38, 4.00	Sorrel	3.27, 2.98, 3.20, 3.13,	3.18, 3.01				
Olives, green, ripe						6.80	Sorrel, cooked	3.60, 3.72, 3.78, 3.80,	3.65, 3.49				
Olives, ripe, processed						6.00	Soy Sauce, Chinese		4.70, 4.80				
Onions, red	5.32, 5.41, 5.39, 5.39, 5.52, 5.39						Spaghetti, cooked	6.40, 6.40, 6.17, 6.27,	5.97, 6.27				
Onions, white	5.48, 5.37, 5.50, 5.59, 5.85, 5.71						Spinach, cooked	7.10, 7.18, 6.60, 6.60,	6.60, 6.65				
Onions, yellow	5.32, 5.47, 5.58, 5.42, 5.32, 5.60						Spinach, frozen, cooked	6.52, 6.37, 6.47, 6.33,	6.30, 6.35				
Onions, pickled						2.71	Spinach, chopped, Clapp	5.52, 5.52, 5.51, 5.52,	5.38, 5.40				
Oranges, Fla., "color added,"							Spinach, puréed, Stokely	5.50, 5.98, 6.22, 5.75,	5.78, 5.78				
Pinellas County	3.90, 3.60, 3.60, 3.63, 3.67, 3.75						Spinach, strained, Clapp	5.70, 5.70, 5.70, 5.70,	5.63, 5.63				
Oranres, Fla., not colored,							Spiritus Frumenti					4.15	
Phillipi River	3.93, 3.69, 4.34, 3.60, 3.88, 3.97						Squash, acorn, cooked	5.61, 5.69, 6.12, 6.49,	5.65, 5.18				
Orange Juice, Californin	4.19, 3.90, 3.59, 3.85, 3.63, 4.34						Squash, Hubbard, cooked	6.15, 6.12, 6.15, 6.00,	6.20, 6.05				
Orange Juice, Florida	4.15, 3.97, 3.30, 3.58, 3.33, 3.49						Squash, white, cooked	5.52, 5.58, 5.70, 5.60,	5.58, 5.70				
Orange Marmalade, com.	3.00, 3.20, 3.23, 3.33, 3.16, 3.14						Squash, yellow summer, cooked	5.94, 5.79, 6.00, 5.98,	5.85, 5.88				
Oyster-plant, cooked	5.72, 5.80, 5.75, 5.80, 5.75, 5.79						Strawberries, California	3.32, 3.50, 3.49, 3.49,	3.45, 3.33				
*Milk, sour, fine curd						5.65, 5.50	Strawberries, frozen	3.32, 3.27, 3.22, 3.22,	3.25, 3.21				
Milk, sour, precipitated curd						5.10, 4.70	Strawberry Jam, com.	3.00, 3.40, 3.33, 3.36,	3.40, 3.36				
Oysters	5.72, 6.10, 6.02, 5.98, 6.17, 5.68						Sweetbreads, broiled		6.70, 6.60, 7.10				
Papaya	5.62, 5.72, 5.50, 5.39, 5.50, 5.20						Swiss Chard, cooked	6.78, 6.28, 6.25, 6.25,	6.30, 6.17				
Papaya Marmalade, com.						4.00, 3.53	Tangerines	4.48, 4.43, 3.93, 4.47,	3.97, 3.32				
Parsley	5.82, 5.97, 6.03, 5.90, 5.62, 5.78						Tomatoes	4.22, 4.75, 4.32, 4.35,	3.99, 4.19				
Parsnips, cooked	5.45, 5.50, 5.65, 5.40, 5.60, 5.61						Tomatoes, local, vine-ripened	4.45, 4.17, 4.17, 4.08,	4.12, 4.02				
Pate de foie, American						5.90	Tomatoes, canned	4.28, 4.10, 4.14, 4.14,	4.14, 4.23				
Peaches	4.05, 3.39, 3.50, 3.30, 3.62, 3.55						Tomatoes, strained, Clapp	4.18, 4.13, 4.13, 4.13,	4.12, 4.12				
Peaches, cooked with sugar						3.55, 3.72	Tomato Juice, canned	4.10, 4.11, 4.14, 4.14,	4.28, 4.28				
Peaches, frozen	3.30, 3.30, 3.28, 3.35, 3.27, 3.32						Tomato Paste, Italian					4.12	
Peaches, canned	3.80, 3.74, 3.73, 3.82, 3.75, 3.70						Tomato Purée, com.	4.10, 4.17, 4.10, 4.10,	4.19, 4.10				
Peach Nectar (pulp, juice, sugar, water), com.						4.03	Tomato Soup, Cream of, canned					4.62	
Peanut Butter						6.28	Tongue, smoked, boiled		6.28, 5.90, 5.77				
Pears, Bartlett	4.08, 4.00, 4.00, 3.69, 3.67, 3.49						Trout, Sea, sautéed	6.32, 6.30, 6.33, 6.20,	6.27, 6.23				
Pears, Sieck, cooked with sugar	4.21, 4.20, 4.09, 4.05, 4.04, 4.09						Tuna Fish, canned	6.10, 6.10, 5.92, 6.12,	6.02, 6.00				
Pears, canned	4.07, 4.03, 4.03, 4.08, 4.00, 4.03						Turnip Greens, cooked	5.91, 5.96, 6.30, 6.21,	6.25, 6.17				
Pear Nectar (pulp, juice, sugar, water), com.						4.13	Turnips, white, cooked	5.82, 5.76, 5.85, 5.65,	5.64, 5.85				
Pea Soup, Cream of, canned						5.72	Turnips, yellow, cooked	5.73, 5.75, 5.70, 5.82,	5.67, 5.57				
Peas, cooked	6.88, 6.61, 6.83, 6.22, 6.35, 6.31						Turkey, roasted	6.80, 6.43, 5.90, 5.72,	7.00, 6.63				
Peas, frozen, cooked						6.62, 6.70, 6.40	Veal Chop, broiled					6.12, 5.90	
Peas, canned	6.00, 5.90, 5.85, 5.71, 5.81, 5.81						Veal Cutlet, breaded					6.80, 5.90	
Peas, puréed, Stokely	4.90, 5.72, 5.85, 5.72, 5.75, 5.75						Veal Kidneys, broiled					6.60, 6.48	
Peas, strained, Clapp	5.91, 6.10, 5.97, 6.12, 6.00, 6.08						Veal, roasted					6.99, 6.74	
Peas, dried (split green), cooked	6.80, 6.50, 6.53, 6.49, 6.45, 6.57						Vegetable Soup, canned					5.16	
Peas, dried (split yellow), cooked	6.62, 6.50, 6.47, 6.45, 6.43, 6.45						Vegetable Soup, chopped, Clapp	5.00, 5.00, 5.00, 5.00,	5.00, 5.00				
Pep	5.85, 5.39, 5.45, 4.49, 4.92, 5.02						Vegetable Soup, strained, Clapp	5.00, 5.00, 5.00, 5.00,	4.99, 4.99				
Peppers, green	5.23, 5.20, 5.93, 5.48, 5.59, 5.54						Vermicelli, cooked	6.50, 6.20, 6.33, 6.40,	5.80, 5.93				
Persimmons	5.42, 5.50, 5.81, 5.55, 5.50, 5.40						Vinegar, cider					3.12	

TABLE II
Effect of dilution on acidity of fruit juices*

	Straight		Diluted 1:1 with water		Diluted 1:5 with water	
	pH	Acid Activity	pH	Acid Activity	pH	Acid Activity
Apple	3.62	2,309	3.78	2,089	3.72	1,906
Cranberry	2.49	29,810	2.60	25,120	2.91	11,450
Grape	3.60	10,990	3.66	8,710	3.13	7,413
Grapefruit	3.25	5,623	3.32	4,786	3.18	4,169
Lemon	2.72	47,860			2.55	28,150**
Pineapple	3.37	4,236	3.46	3,467	3.52	3,020
Tomato	4.10	794	1.15	708	1.20	631

*Commercially canned.

**Diluted 1:10 with water, otherwise unpalatable.

(in terms of actual acidity) than the preceding; yet the pH scale shifts slowly downward toward a hypothetical zero with a regular "arithmetic" progression. Consequently, the change in acidity is far greater between 3 and 4 than between 6 and 7 (from the pH

scale, the change would seem to be identical). Furthermore, the midpoint does not occur at 0.5 on the pH scale, but at 0.3. For instance, pH 6 is ten times as acid as pH 7, pH 6.5 is but slightly more than three times as acid, whereas 6.3 is five times as acid as pH 7 (see Table V). Likewise, pH 4.8 and 4.9 are nearer to each other in actual acidity than 4.1 and 4.2, all of which makes comparison of pH values difficult for the uninitiated. Although it must be granted that pH values are easier to inspect, they are much harder to interpret than hydrogen-ion concentrations.

Unfortunately, acid concentration directly expressed involves mathematical forms with which many are unfamiliar. To remedy this difficulty and make comparison easy, Tables V and VI have been introduced. Although much of the information in these tables is similar to that offered by Wherry (15), the fundamental reasoning is very different. If the term, *Acid Activity*, (which has no meaning with reference to these or any other data except as specifically stated) is multiplied by 10^{-7} (that is, by 0.0000001) the result will be hydrogen-ion concentration in gram-equivalents per liter. Since this understood factor is the same throughout, evaluation of the corresponding

TABLE III
pH of recipe foods and soda fountain items

Item	pH	Item	pH
Barley Soup	5.63	Ice Cream:	
Blanc Manger	6.33	Caramel Pecan	6.18
Bread Pudding, plain	5.40	Cherry	5.18, 6.18, 6.11, 6.12, 6.05, 6.16
Bread Pudding, chocolate	6.40	Chocolate	5.59, 5.53, 5.49, 5.88
Broth, beef, clear	5.54, 5.10	Coffee	6.23
Broth, beef, with rice	6.10, 5.62	Strawberry	5.60, 5.67
Broth, chicken	6.21	Vanilla	6.34, 5.25, 5.40, 6.53
Butterscotch Sauce	5.20	Ice Cream Sodas:	
Cake, plain	6.59	Chocolate	5.80
Celery, creamed	6.00	Coffee (whipped cream)	5.84
Celery Soup, cream of	6.30	Pineapple (no milk)	4.95
Cheese Fondue	5.35	Strawberry, plain	4.75
Cheese Ravioli	5.04	Same with milk	5.20
Chow Mein, beef	5.76	Lemonade	2.75, 2.70
Chocolate Beverage		Limonde	2.56
($\frac{2}{3}$ milk and $\frac{1}{3}$ cream)	6.28, 6.32	Malted Milk, chocolate	6.48
Chocolate Beverage (condensed milk)	6.03	Malted Milk, chocolate (thick)	6.52
Clam Chowder, Manhattan	5.20	Malted Milk, chocolate, with egg	6.70
Club Soda, "supercharged"	4.20	Muffins, bran	6.32
boiled to remove CO ₂	7.55	Mushroom Soup, cream of	6.07
Cocoa Beverage	6.15, 6.18	Noodle Soup	3.82, 3.85
Coca Cola, bottled, N.Y.C.	2.49, 2.65, 2.30, 2.56, 2.50, 2.58	Orangeade	3.75
Coca Cola, fountain		Orange juice base	6.17
Plain	2.16	Pea Soup, cream of	6.05, 6.09
With fresh lemon	2.78	Pea Soup, split green	5.52
Plain	2.62	Postum, beverage	5.42
With fresh lemon	2.12	Postum, beverage, clear	6.03
Lemon juice used	2.28	with 20% cream	6.17
Coffee, clear	4.83, 4.74, 4.83, 5.04, 4.78, 4.80	with evaporated milk	6.23
Coffee, clear	4.97	with milk	5.35
with 20% cream	5.62	Postum, beverage, clear	6.20
with milk	6.00	with 40% cream	5.90
with evaporated milk	5.00	Potatoes, Idaho, baked (with butter)	5.23, 6.62, 6.30, 5.78, 6.02, 5.80
Coffee, clear	5.23	Potatoes, Irish, baked (with milk)	5.90, 5.98, 5.90, 5.92, 6.15, 6.18
with 10% cream		Potatoes, Irish, boiled	5.58, 5.55, 5.91, 5.80, 6.02, 5.23
Coffee, Harrington House (soluble)		Potatoes, Irish, boiled (with milk)	6.03, 6.00, 5.93, 6.08, 6.22, 5.70
clear	5.10	Potatoes, Irish, mashed	
with cream	5.90	(with milk and butter)	5.83, 5.93, 5.90, 5.90, 5.80, 5.89
clear	5.32	Potatoes, Sweet, baked (with butter)	5.35, 5.31, 5.29, 6.20, 5.70
with cream	5.78	Potatoes, Sweet, boiled (with butter)	6.00, 5.88, 6.04, 5.98, 6.12, 5.98
clear	5.10	Potatoes, Sweet, canned	5.10
with condensed milk	6.20	Rice Pudding	5.41, 6.30, 6.50
Coffee, G. Washington's Acres (soluble)		Russian Dressing	4.93
clear	5.20	Scone, Scotch-style	7.01
with cream	5.78	Spinach Soup, Cream of	6.21
clear	5.22	Tamarind, brewed	2.75, 2.60, 2.82, 2.79, 2.78
with milk	6.01	Tapioca Pudding, caramel	6.16
clear	5.18	Tea, Orange Pekoe type (weak)	6.97, 6.83, 5.30, 5.60, 6.10, 6.65
with condensed milk	6.10	Tea, Orange Pekoe type (medium)	6.51, 6.43, 5.27, 5.18, 6.25, 6.91
Coffee, Sanka	6.10	Tea, Orange Pekoe type (strong)	5.76, 5.90, 5.13, 4.98, 6.25, 5.79
Corned Beef Hash (with potatoes)	5.26	Tea, clear	5.80
Corn Soup, cream of	6.18	with lemon	3.40
Continental, baked	6.75, 6.50, 6.70	with 40% cream	5.20
Egg nog	6.58	Tea, clear	5.27
Eggs, omelette	7.70	with lemon	4.40
Eggs, scrambled (milk and butter)	7.23, 7.34	with 20% cream	6.25
Frosted Drinks:		with evaporated milk	6.30
Chocolate	6.33, 6.33	with milk	6.43
Strawberry	5.82	Tomato Soup, Cream of	5.62
Ginger Ale, Canada Dry	2.75, 2.71, 2.76, 2.78, 2.78, 2.68	Vegetable Soup	5.40, 5.45
Ice Cream, Plain mix		Vegetable and Barley Soup	4.47
(Tested at Herten plant)	6.58	Vegetable-Okra Soup	5.05
Ice Cream, chocolate mix		Water, Sparkling, Canada Dry	5.15, 5.16, 5.35, 5.28, 5.59, 5.42
(Tested at Herten plant)	6.42	Water, "White Rock"	4.90, 4.76, 4.36, 4.25, 4.99

TABLE IV
Variation in pH of eggs with age

Age	White	Yolk
2 hours	6.58 7.03	7.0 6.88
12 hours (or less)	6.70	7.00 6.60
24 hours	6.62 6.60	6.50 6.10
48 hours	7.43 7.87	6.80 6.29
'New-laid' store eggs	7.72 7.72	6.18 6.61
Coldest storage eggs	7.50 7.60 7.60 7.68 7.72 8.20 7.90 7.62	6.00 6.87 6.90 6.80 6.90 6.00 6.63 6.00 6.60
		7.00 6.90 6.78 6.72 6.82 7.50 7.20

Data carried across table represent analyses on the same egg, the white and yolk being mixed after separate testing.

pH values is readily undertaken. For example, how much more acid is lime juice at pH 2.0 than orange juice at 3.6? From Table V it will be seen that lime juice is roughly forty times as acid as orange juice since their *Acid Activities* are 100,000 and 2,512 respectively.

To conserve space, Table V presents data only at 0.1 pH intervals. Where closer readings are desired, Table VI shows the variation encountered with changes of 0.01 pH. Since the "whole number" in the pH value designates merely the position of the decimal point, the corresponding *Acid Activity* can be obtained by using the numerical sequence in Table VI and placing the decimal as indicated in Table V. For example, *Acid Activity* for a sample of plum juice at pH 4.32 is desired. The 4 is ignored and the 32 is found in Table VI under 6.32 as equivalent to 4,786. Since pH 4.32 lies between 4.3 and 4.4 which are 501.2 and 398.1 respectively, its *Acid Activity* becomes 478.6 or approximately 480.

If, then, anyone especially desires to have the "average" pH of any food from the series of determinations offered in Table I, it will be necessary to compute the *Acid Activity*, average these numbers, then read back to the corresponding pH.

CHEMICAL DISCUSSION

Although the food was sampled so as to obtain as wide a variation as possible, nevertheless it is likely that some of the values are not typical. Many unknown factors, such as climatic and soil conditions as well as difference in processing, affect the pH. The influence of artificial maturing as against natural ripening has not been studied although one such contrast is offered under tomatoes. The local, vine-ripened

fruit was far superior in flavor or "sweetness" to the poorly-colored forced variety, yet it was somewhat more acid (average *Acid Activity* of 709 against 516).

Effort was directed at analyzing the various food products as their seasonal periods arrived. Since it was desired to secure data covering a wide range, testing was not restricted to the articles of diet expected on hospital menus but was extended, through private channels, to items of special interest. This policy will be pursued, as opportunity affords, in an attempt to encompass the complete gamut of edible substances.

Data on some items will not be found since acceptable values were not obtained. Butter, oil and vinegar, and other fatty mixtures were troublesome to test. Two samples of salted butter which had been melted and cooled read pH 5.40 and 6.28, but these figures are not believed to be entirely trustworthy. Again, a substance like water does not yield satisfactory results on the pH meter due largely to "drifting." Readings for tap water varied from pH 6.0 to 7.5.

The point on the pH scale at which hydrogen- and hydroxyl-ions equal each other, namely 7.0, is devoid of practical meaning. The sharp separation of solutions below 7 from those above it into acid and alkaline respectively is a wholly artificial device. The chemist largely disregards this theoretical neutral point and establishes new and different "neutral"

TABLE V
Acid activity over pH range of foods reported*

pH	Acid Activity	pH	Acid Activity	pH	Acid Activity
9.0	0.010	6.6	2.51	4.2	671.0
8.9	0.013	6.5	3.16	4.1	794.4
8.8	0.016	6.4	3.98	4.0	1,000.0
8.7	0.020	6.3	5.01	3.9	1,258.9
8.6	0.025	6.2	6.31	3.8	1,584.9
8.5	0.032	6.1	7.94	3.7	1,995.3
8.4	0.040	6.0	10.00	3.6	2,511.9
8.3	0.050	5.9	12.59	3.5	3,162.3
8.2	0.063	5.8	15.85	3.4	3,981.1
8.1	0.079	5.7	19.95	3.3	5,012.0
8.0	0.100	5.6	25.12	3.2	6,310.0
7.9	0.126	5.5	31.62	3.1	7,943.3
7.8	0.158	5.4	39.81	3.0	10,000.0
7.7	0.200	5.3	50.12	2.9	12,589.3
7.6	0.251	5.2	63.10	2.8	15,849.0
7.5	0.316	5.1	79.43	2.7	19,953.0
7.4	0.398	5.0	100.00	2.6	25,119.0
7.3	0.501	4.9	125.89	2.5	31,622.8
7.2	0.631	4.8	158.49	2.4	39,811.0
7.1	0.794	4.7	199.53	2.3	50,118.7
7.0	1.000	4.6	251.19	2.2	63,100.0
6.9	1.259	4.5	316.23	2.1	79,433.0
6.8	1.585	4.4	398.11	2.0	100,000.0
6.7	1.995	4.3	501.19	1.9	125,893.0

*If the decimal point of *Acid Activity* is moved seven places to the left, the resultant value will be hydrogen-ion concentration (g/liter).

TABLE VI
Variation in acid activity* over a pH unit

pH	Acid Activity	pH	Acid Activity	pH	Acid Activity	pH	Acid Activity
7.00	1.000	6.75	1.778	6.50	3.162	6.25	5.623
6.99	1.023	6.74	1.820	6.49	3.236	6.24	6.754
6.98	1.047	6.73	1.862	6.48	3.311	6.23	6.888
6.97	1.072	6.72	1.906	6.47	3.389	6.22	6.026
6.96	1.097	6.71	1.950	6.46	3.467	6.21	6.166
6.95	1.122	6.70	1.995	6.45	3.548	6.20	6.310
6.94	1.148	6.69	2.042	6.44	3.631	6.19	6.467
6.93	1.175	6.68	2.089	6.43	3.715	6.18	6.607
6.92	1.202	6.67	2.138	6.42	3.802	6.17	6.761
6.91	1.230	6.66	2.188	6.41	3.890	6.16	6.918
6.90	1.259	6.65	2.239	6.40	3.981	6.15	7.080
6.89	1.288	6.64	2.291	6.39	4.074	6.14	7.244
6.88	1.318	6.63	2.344	6.38	4.169	6.13	7.413
6.87	1.349	6.62	2.399	6.37	4.266	6.12	7.586
6.86	1.380	6.61	2.455	6.36	4.365	6.11	7.763
6.85	1.413	6.60	2.512	6.35	4.467	6.10	7.944
6.84	1.446	6.59	2.570	6.34	4.571	6.09	8.128
6.83	1.479	6.58	2.630	6.33	4.677	6.08	8.318
6.82	1.514	6.57	2.692	6.32	4.786	6.07	8.511
6.81	1.549	6.56	2.754	6.31	4.898	6.06	8.710
6.80	1.583	6.55	2.818	6.30	5.012	6.05	8.913
6.79	1.622	6.54	2.884	6.29	5.129	6.04	9.120
6.78	1.660	6.53	2.951	6.28	5.248	6.03	9.333
6.77	1.698	6.52	3.020	6.27	5.370	6.02	9.550
6.76	1.738	6.51	3.090	6.26	5.495	6.01	9.772

*If the decimal point of Acid Activity is moved seven places to the left, the resultant value will be hydrogen-ion concentration (g/liter).

points as necessitated by the type of chemical change under experimentation. The physiologist has still less use for pH 7 since biochemical processes are limited to definite concentrations of hydrogen-ion without regard for the absolute neutral point. Gastric digestion, for instance, proceeds normally at pH 1.6-1.8; when this value reaches pH 3, the condition is described as an acidity. On the other hand, pH 7.2 is decidedly acidotic so far as blood plasma is concerned. Furthermore, litmus paper reacts "alkaline" below pH 7 so causing urine samples to be reported as alkaline when in reality they are on the acid side of neutrality. Extreme acidity in the stomach necessitates a pH of approximately 1.2; extreme acidity is reached in the urine at pH 4.6; fatal acidosis is encountered before the blood falls to pH 7. Each of these body fluids has its own normal or what might be termed "neutral" point from which it varies toward a relatively more acid or alkaline state. Each "acid-base" relationship is balanced about an individual point which is wholly unrelated to absolute neutrality (pH 7).

As might be expected, those foods acid to the taste are far down the pH scale. Those disagreeably acid to all palates approximate pH 2. Above pH 5, in general, and above pH 4 not infrequently, foods can be described as neutral to the tongue. *Insofar as they do not induce further secretion of gastric acid*, foods showing pH values greater than 5 are essentially

"alkaline" in the stomach. It is not possible by introducing into the stomach a food acid to produce an alkaline reaction as is so frequently claimed for the citrus fruits. Any alkalinity attributable to these fruits is dependent upon the oxidation of the citric acid to carbonate after absorption has occurred.

Very few foods are found to be alkaline. The only common ones consistently so in our experiments were graham crackers and cold storage eggs. Egg-white, shrimp, lobster and conchs were invariably alkaline. Occasionally, soda crackers, sweetbreads, duck, clams, cantaloupe, fresh spinach, and fresh or frozen corn

TABLE VII
Comparison of pH values on some raw and cooked vegetables

Item	Raw	Cooked
Cabbage, green	5.79-6.29	6.38-6.82
Cabbage, red	6.43-6.00	6.21-6.42
Carrots	5.96-6.00	6.58-5.88
Celery	6.86-6.00	5.37-5.92
Fennel	5.48-5.88	5.80-6.02
Leeks	5.51-6.07	6.79-6.16
Sorrel	2.98-3.27	3.49-3.80

reached or exceeded pH 7. The rapid shift of whole eggs to an alkaline reaction is shown in Table IV.

The cereals and cereal products which are so widely used in ulcer diets do not fall below pH 5 as a rule, except in obvious instances as pumpernickel bread (pH 4.4). It should be stressed that the cereals were tested with addition of just enough water to moisten them. As consumed, more or less generous amounts of milk accompany the cereal and tend to raise the pH although it will be seen that many of these breakfast foods already exceed pH 6.

The introduction of milk or cream into a beverage or soup raises its pH as might be anticipated. This is demonstrated in Table III under coffee, tea and chocolate beverages. It is also obvious in the various soda-fountain drinks. A strawberry ice cream soda of pH 4.75 is elevated to 5.20 by introduction of the customary "shot" of milk; the strawberry ice cream in this instance was pH 5.60. Due to the fruit acid, a strawberry "frosting" (or milk shake) is more acid than a chocolate one (pH 5.82 and 6.33, respectively). The introduction of malt or egg raises the pH still further.

With the exception of tomato, the "home-made" cream soups were found to approximate pH 6.2; the corresponding canned products were more acid (as cream of pea, pH 6.17 and 5.72 respectively; cream of mushroom, pH 6.20 and 5.95; and cream of tomato, pH 5.62 and 4.62). In this connection it is interesting to note the reaction of broth since it is well recognized that broth is clinically contra-indicated in cases of gastric hyperacidity. It is obvious, however, that the detrimental factor cannot be the pH of the broth.

Although plain gelatin gives a pH of 6.08, its preparation as a dessert involves the introduction of fruit acids so that the finished product is apt to be pH 3. Regardless of the fruit used, preserves and jellies usually vary from pH 3 to 4.

Honey is noteworthy in that it shows a pH of 3.8 in contrast with Karo and maple syrups at pH 4.5 and 5.15, respectively.

In general, the vegetables vary from pH 5 to 7. Exceptions are tomatoes between pH 4 and 5, and sorrel and sauerkraut which are more acid than pH 4.

Canned vegetables and fruits also proved to be more acid than those freshly cooked.

	Asparagus	Beets	Peas	Corn	Carrots
Fresh	6.03-6.16	5.23-5.90	6.22-6.88	6.22-7.04	5.58-5.88
Canned	5.20-5.32	4.92-4.98	5.71-6.00	5.90-6.44	5.15-5.22

The frozen products have been found to be close to the reaction for the fresh-cooked vegetables with a definite tendency toward greater alkalinity.

Although practically no experiments were conducted to demonstrate the type of change involved in cooking, there appears to be a definite tendency toward greater alkalinity on boiling a food. In one instance, a sample of tomatoes was found to be pH 4.20; after it was stewed, the value was 4.32. Data on vegetables eaten both raw and cooked have been assembled in Table VII, but it must be stressed that the tests were conducted on totally different samples and so are not strictly comparable.

Bananas, figs, papayas, persimmons and water-melons are less acid than most fruits and vary between pH 5 and 6. Melons of the cantaloupe type and avocados exceed pH 6 and may even be alkaline. The acid character of the fruits, however, is reflected in the pH encountered with the vast majority. With the exceptions noted, fresh, cooked and canned fruits vary from pH 3 to 5. Those below pH 3 include some of the grapes, plums and occasional samples of grape-fruit juice. Cranberry juice is usually more acid than pH 2.5 while limes and lemons are close to pH 2. Although it is possible that the tamarind, a tropical legume, is the most acid of our fruits, beverages made from it were found to vary from pH 2.60 to 2.82. Fruit drinks below pH 2.5 are rarely acceptable. Acidity greater than pH 3 renders a fruit unpalatable to many individuals.

The reaction of the representative foods examined is best visualized with a frequency distribution curve (Fig. 1). Over 70 per cent of the items tested are characterized by values between pH 5 and 7 and are

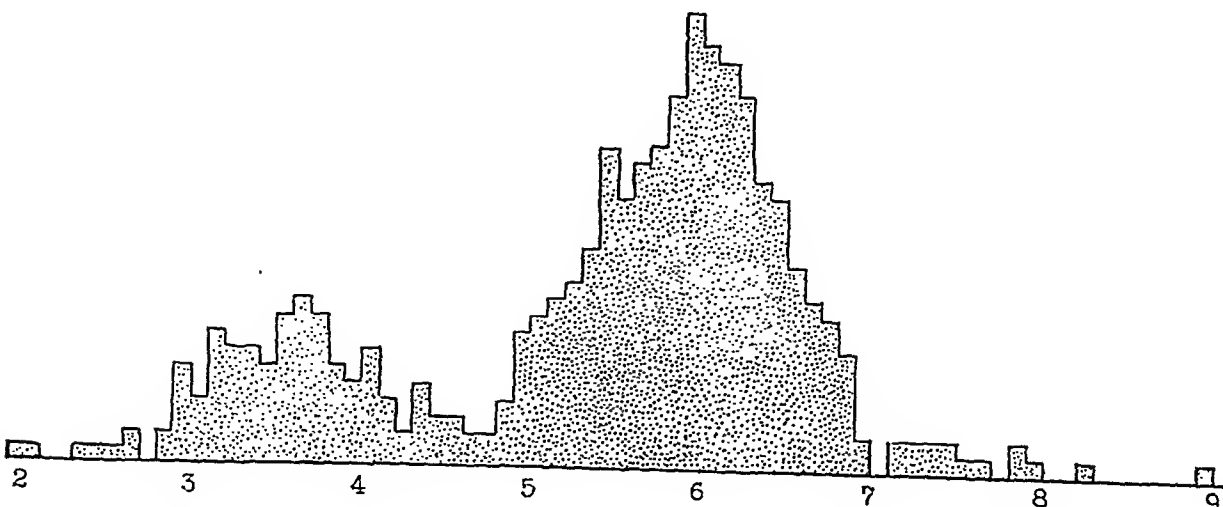


Fig. 1. Frequency distribution curve constructed from typical values for each food item.

distributed almost equally on either side of pH 6 (the upper group exceeds the lower by 3 per cent). Only 2 per cent are more acid than pH 3. Less than 3.5 per cent are alkaline. Strangely enough, the range between pH 3 and 4 covers twice as many items as that between pH 4 and 5, namely, 16 and 8 per cent respectively.

In Table II the effect of dilution of a fruit juice with water appears to be small from the standpoint

TABLE VIII

The effect of orange juice on sippy diet mixtures

Food Mixtures	pH
Cream, 20%	6.60
3 t. cream + 1 t. orange juice	5.00
Farina with 20% cream	6.70
3 t. cream-cereal + 1 t. orange juice	4.93
Beaten egg with 20% cream	6.90
3 t. cream-egg + 1 t. orange juice	5.85
Orange juice used throughout	3.75

of pH, yet if this data is recast in terms of actual acidity, the change is obviously considerable. This table demonstrates how difficult it is to judge acidity merely from pH values.

CLINICAL DISCUSSION

It is possible that the future will demonstrate that the pH of the food per se is of little moment. Presumably the most important factor is the property of the individual food in stimulating the flow of gastric juice whether this be attributable to hydrogen-ion, to other constituents in the food, or to products of digestion.

Actually few substances are introduced into the stomach which can compete with the acidity of HCl. Only 2.9 per cent of all the foods tested showed values less than pH 3. None approximated normal gastric acidity at the height of digestion (pH 1.6-1.8). Those foods which reach the level of low gastric acidity (pH 2.0-2.4), as lemons and limes are rarely consumed as such. The immediate physical effect of introducing food into the stomach, be the food highly acid or not, is to dilute the gastric juice and so diminish the acidity, but the normal response to the presence of food is secretion of sufficient HCl and pepsin for the digestion thereof. Consequently, the ultimate result may be increased acidity regardless of the original reaction of the food.

Although foods vary in their ability to stimulate the flow of gastric juice, this effect is largely an individual matter so that generalizations are more or less meaningless when applied to specific cases. The gastric response depends upon idiosyncrasy of taste, varies with the whim of the subject during health, and is markedly altered during illness. Fatigue, nervous strain, mental abnormalities and the like may occasion unusual and unexpected variation in gastric behavior.

Because of the psychic, thermal, mechanical and other stimuli of dining, it is difficult to determine the precise behavior of foods under reproducible conditions. Even water will stimulate the flow of gastric juice. The hyperacidity associated with over-ingestion of water in diabetes insipidus is a case in point. Coffee

and tea are both associated with increased gastric acidity. Alcoholic beverages, in small amounts, induce acid secretion although gastric hypoauidity is common among chronic alcoholics. Tobacco is in no sense a food adjunct, but smoking in moderation stimulates production of hydrochloric acid. Extremely hot or cold foods have an irritating action upon the stomach which may result in increased acidity.

The level of the gastric acid is believed by some to be related to the blood sugar. Administration of insulin produces hypoglycemia and also stimulates the flow of hydrochloric acid. It has yet, however, to be conceded that hyperacidity universally accompanies hypoglycemia and vice versa, although excellent clinical results have been secured by avoiding the reduction of blood sugar in patients with excess gastric acid.

The most abundant and best sustained secretion of acid is achieved with meat, partially digested protein being the exciting agent. Broths, meat extracts and stock soups as well as gravies elevate gastric acid. Smoked and brined foods, mustard, pepper, horseradish, chili-sauce, salad dressings, pickles, garlic, sweet herbs, spices, mushrooms (an otherwise useless food), and fruit flavors as well as aromatic substances characteristic of many of our foods and beverages add to the zest of eating and act as gastric stimulants. New, unfermented cider is thought to be one of the strongest acid-producers (16). From clinical experience, the leafy vegetables have proved somewhat acid-stimulating. The effects have been attributed to the presence of organic acids.

In this connection the conclusion of Dimmler (13) should be cited:

"Judging from some observations made in vitro it seems probable that one need not worry about giving orange juice to patients who have peptic ulcer. If the orange juice should remain in the stomach long enough to have any effect on the acidity of the gastric content, this effect almost certainly would have to be a lowering one because orange juice is considerably less acid than is even normal gastric juice."

TABLE IX

The effect of Cevitamic Acid on ulcer-diet mixtures

Food Mixtures	pH
Cevitamic Acid Solution I (50 mg.) suspension in 50 ml. water	3.42
Cream, 20%	6.53
4 t. cream + 5 ml. Solution I	6.52
Cevitamic Acid (50 mg.) in 10 ml. cream	5.70
1 t. Farina + 2 t. cream	6.72
with 5 ml. Solution I	6.62
Beaten egg	7.48
4 t. egg + 5 ml. Solution I	7.30

Although in vitro experiments have demonstrated that addition of orange juice to gastric fluid diminishes the acidity of the latter by dilution "according to what any chemist would have expected" (Alvarez), the stomach is not a glass beaker. Symptomatically, citrus fruits intensify gastric acidity.

The irritating action of citrus fruits in ulcer cases is so well known that these patients are routinely de-

prived of this source of Vitamin C for long periods of time. Orange juice on an empty stomach is scarcely to be recommended for ulcer patients, yet sufficiently, "buffered" by the various constituents of the Sippy diet enough of this fruit juice presumably could be given to avoid development of Vitamin C deficiency. In a few experiments (Table VIII) relatively large amounts of orange juice were employed to ascertain its influence on the reaction of the food pH—although it must be stressed repeatedly that the pH of the mixture is not the sole factor determining the effect in the stomach.

A single 50 mg. tablet of Squibb cevitic acid in

a minimum of water was observed to be pH 3 whereas a suspension in 50 ml. of water was found to be pH 3.42. This solution when introduced into ulcer-diet foods resulted in the alteration of pH shown in Table IX.

SUMMARY

1. In tabulated form 2,100 determinations of the pH of over four hundred representative foods have been presented.
2. Data are given for what is termed "Acid Activity" and its use in evaluating pH results is shown.
3. The clinical value of food reaction is given brief comment.

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Phenolphthalein as a Test for Gastro-Intestinal Ulceration in the Experimental Animal*

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OUR interest in the experimental production and treatment of peptic ulcer led us to determine the usefulness of the Woldman test (1) for ulceration of the stomach and duodenum in the laboratory animal. In the dog peptic ulcer can be said never to occur spontaneously, only under experimental conditions such as follows the administration of cinophen, ligating the common bile duct, after the Mann-Williamson operation, etc. It seemed that the Woldman test would be a simple means to indicate or confirm the presence of gastro-intestinal ulceration in the dog. In attempting to evaluate this test 37 determinations were made on normal dogs and on dogs known to have ulceration. The tests were divided into four groups.

Group I. In this series the same technique was used as described by Woldman (1). Each fasting dog received 10 cc. of 1% phenolphthalein diluted to 30 cc. with water and administered by stomach tube. The dogs were catheterized at the end of 1 hour and 2 hours. The urine was tested with 10% Sodium Hydro-

xide. As indicated, with this dose there was no uniformity of results.

	Positive	Negative
6 normal	3	3
1 cinophen (ulcer)		1
2 common duct ligation (ulcer)	1	1

Group II. The phenolphthalein was reduced to one-half the dose used in the first series in attempting to eliminate the false positive results. Paradoxically, the four normal dogs used all had positive reactions on the reduced dose. At this time it was found that the urine of all jaundiced dogs gave a positive reaction. Further investigation revealed that the urine of jaundiced dogs not receiving phenolphthalein gave a color ring similar to the phenolphthalein color ring on the addition of alkali. This is apparently due to the action of the alkali on the bile pigments and may account for the 100% positive tests obtained on jaundiced patients by Steigmann and Dyniewicz (2).

	Positive	Negative
4 normal	4	
2 cinophen (ulcer)		2
2 common duct ligation (ulcer)	2	

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Group III. The unsatisfactory results in the second group led us to calculate the same dose per kilo of weight for the dog as for a man weighing 70 kilos receiving 10 cc. of 1% phenolphthalein. This method seemed the nearest approach to the proper dosage.

	Positive	Negative
14 normal	2	12
1 common duct ligation (ulcer)	1	

Group IV. In this group acute surgical ulcers were produced in five dogs. These ulcers were made by removing a patch of mucosa near the pyloric end of the stomach at least 2 cm. in diameter. The tests were made 2 days after operation. The dose of phenolphthalein was calculated by the same method as in series III. Despite the large size of the ulcers no phenol-

phthalein was found in the urine of 3 of the 5 dogs.

	Positive	Negative
5 acute surgical ulcers	2	3

CONCLUSION

We were unable to determine the exact dose of phenolphthalein to give uniform results. We found that dogs with jaundice gave false positive reactions. The fact that the test was variable in acutely produced ulcers would seem definitely to exclude it as a test for determining the presence of ulceration of the gastrointestinal tract in the experimental animal.

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Anal Cryptitis

By

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THE mucous membrane of the lower part of the rectal ampulla is thrown into longitudinal folds as the lumen of the bowel narrows to the anal canal. This folding of the mucosa permits snug closure of the anus when the sphincters are contracted, and also accommodates itself to full dilatation without injurious stretching, when the anus is opened for the passage of feces or for instrumentation. These folds are known as the columnae rectales or Columns of Morgagni and end about one-half inch up from the anal orifice at what was the fusion of the hind gut with the proctodeum. Between each two folds there is a depression of the mucosa, the lower end of which terminates in a cup-shaped pocket, known as an anal pocket or crypt of Morgagni. The mucosa at the lower end of this interfold depression is loosely puckered into a semilunar fold, which very much resembles the semilunar valve of the heart, and is often referred to as an anal valve. Some of these crypts are but slight depressions, while others form distinct sinuses. These crypts mark the termination of the mucosa lined rectum and the beginning of the cutaneous lined anal canal. They secrete a thick mucus which serves to lubricate the fecal mass just before its extrusion from the anal canal. They vary from three to twelve in number and are recognized as openings in the mucous membrane, usually crowned by small papillae.

The fecal mass, at this juncture, has to overcome the contraction of the external sphincter muscle; hence, the necessity of some sort of lubrication at this part of the canal. Since the function of these crypts is so essential, it is important to be able to recognize a healthy crypt from a diseased one. Otherwise, great injury may be done to the function of defecation by removing healthy crypts.

PATHOLOGY

The crypt's mouths, being directed upwards, it is very easy for substances coming down through the

anal to lodge in the crypts and irritate them. It may be hardened feces, fecoliths, seeds, needles, pins, or any hard substance with a sufficiently small point to lodge in the crypt.

When hardened feces become lodged in a crypt, the tendency is to collect additional feces, until the pressure becomes so great that irritation is set up, finally resulting in pressure necrosis and thus exciting a cryptitis that may become chronic; or a persistent ulceration may result, that, if left untreated, may cause a fissure or go on to abscess and a final fistula.

If the pressure is not sufficient to cause necrosis and ulceration the irritating mucus secreted may burrow down subcutaneously, forming a sinus with a large skin tab externally. If the irritating mucus passes out at the muco-cutaneous border, an excoriation will result. Also the inflammation of the crypt will cause hypertrophy of the neighboring papilla, the composite irritation later causing spasticity of the external sphincter and sphincteralgia. The pathologic changes are often of a low grade and cryptitis has been looked upon by some as a neurosis being referred to at times as "an insane rectum."

These pockets being at the upper margin of the internal sphincter have their circulation interfered with by spasm and the presence of varicose veins. Frequently cryptitis is an extension of a proctocolitis or the internal opening of a fistula. The lower border of the crypt is anal skin and its sensory nerves account for the pain. While an extensive proctitis is not uncommon, the first and greatest reaction is usually in the crypts and they are the last to clear up. An acute cryptitis may become chronic. A patient may or may not complain of soreness. This low grade infection invades the submucosa and weakens the veins and their supporting tissues to such an extent that hemorrhoids develop or prolapse of the mucosa occurs. The infection burrows down beneath the anal skin and its sagging from loss of tone, results in the formation of the well known skin tags which in themselves are of

no consequence except that their presence suggests chronic inflammation above.

The infection from a crypt may gradually burrow down beneath the anal skin and weaken it so much that a slight overstretching causes a tear and a fissure results, just as old rubber which has lost its elasticity cracks when stretched. Most fissures occur posteriorly because the posterior quadrant is subject to the greatest stretching where the sphincter muscle is weakest. The fissure may fail to respond to treatment and even though it heals will break open repeatedly because it is secondary to the infection of the crypt. It will usually not remain healed permanently until the infected crypt is removed, the fissure excised and the subcutaneous tissues about it thoroughly drained.

SYMPTOMS

This area, known as the anorectal line, *linea dentata*, or pectinate line is of special interest because it is the seat of inflammatory changes which produce symptoms apparently out of all proportion to the lesion.

There are no symptoms definitely referable to cryptitis but only those characteristic of inflammatory disease in the anal canal, of which pain in some degree or type is always present.

A constant, dull, aching pain in the anus or rectum is the usual symptom, being accompanied often with a feeling of heaviness. This pain is increased during defecation, following strenuous exercise or prolonged standing, and is relieved by sitting or by pressure on the perineum. If abscess threatens, the pain becomes so intense that the condition may be mistaken for anal fissure or neuralgia of the rectum.

A low-grade, chronic inflammation may involve all the tissues of the anal canal and the aching pains may radiate to the sacrum, down the legs (resembling sciatica), or may simulate sacro-coccygeal neuralgia. It is this class of patients who suffer with "coccygodynia" which may be a true arthritis of the sacro-coccygeal joint. The coccyx may appear normal but the slightest movement or pressure on the sacro-coccygeal joint causes intense pain.

Reflex pain and spasm of the neck of the bladder may cause prostatic irritation frequent micturition or urinary retention, and thus prostatic disease is erroneously diagnosed, or, in the female, dysmenorrhea or amenorrhea may throw suspicion on the generative organs.

If the inflammation remained confined to the mucus coat of the bowel, there would be comparatively little trouble in eradicating it but, unfortunately, the infection often involves the arcolar and muscular coats and even extends to the perirectal tissues. In this manner not only are sacks or ulcerating pouches formed, but sinuses burrow various distances up the bowel or outward under the perianal skin, causing an itching, not relieved by scratching, though not a true pruritus. These septic foci constitute a frequently overlooked cause of pruritus ani. As the mucus is imprisoned in these sinuses, the overlying structures—mucosa and skin—become puffy and more or less sensitive. If the accumulated excretion is confined beneath a thin layer of tissue, it is easily recognized during the examination. When fecaliths or other foreign substances become lodged in a crypt, they may cause excessive itching or pain, until removed by the passage of feces or are scooped out by the surgeon.

Pain in some form—usually sphincteralgia—is the most frequent complaint for which patients apply for treatment. Inflammation and edema of the mucosa cause contraction of the sphincter, and the spasm of the sphincter increases the pain. A burning, stinging pain is usually due to hypersecretion of mucus. If a complete fistula exists, the irritating discharge will cause an excoriation of the mucosa and the perianal skin. Sometimes, if the discharge is excessive, the anal margins may be glued together.

These patients, are decidedly neurotic, complaining of insomnia, despondency, flatulence, intercostal pain, so-called muscular pain in the arms or legs, headache, attacks of dizziness, sometimes accompanied with nausea. All these symptoms indicate toxic absorption from a focal infection. Too often when an examination of the eyes, teeth, tonsils and sinuses is negative the sufferer is classed as one of intoxication due to chronic constipation and treated for intestinal

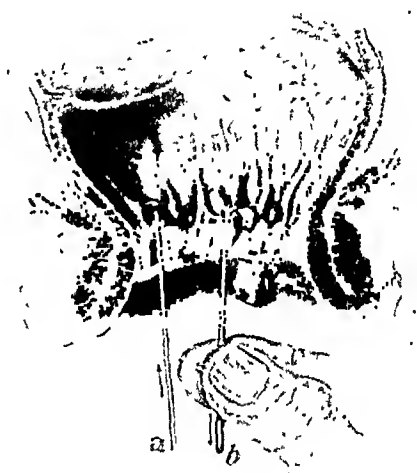


Fig. 1. Searching out the anal crypts.

indigestion. Such low grade infection may be associated with infected crypts or hypertrophied fibrous papillae.

DIAGNOSIS

With a history of the above symptoms, cryptitis should be suspected and a careful examination made. Upon digital examination the inflamed area may be located by its exquisite tenderness. A fenestrated conical speculum should then be introduced, the window slowly rotated, and each crypt or pouch fully exposed and carefully explored for the lodgement of foreign bodies or ulcerations. With a fine straight probe, every crevice or depression in an upward direction is explored, while a bent probe searches all recesses extending downward (Fig. 1). The probe should be of silver, very fine, and should offer no resistance to the tissue. It should be remembered that a probe may easily be introduced into a crypt and through its walls into healthy tissue beyond.

If a crypt is inflamed or a channel discovered, the introduction of the probe will occasion severe pain and the patient will flinch and cry out. It is therefore necessary to minimize this suffering by applying a pledget of cotton soaked in a 10 per cent solution of

cocaine. Local anesthesia should, however, be resorted to only in extremely nervous patients, as the anesthesia will obscure the condition of the crypts. The probe, introduced into a healthy crypt causes very little pain, while an inflamed crypt is very tender. This sensitiveness is often the only criterion of a deviation from the normal, so it is easy to see how anesthesia may cause the examiner to overlook mild or beginning cryptitis, by obscuring the evidence—pain on probing. If there is much sphincter spasm the sphincter must be desensitized. This can be done by infiltrating the muscle with $\frac{1}{2}$ per cent solution of Novacaine. The patient may sometimes be able to assist in locating the diseased area by directing attention to the part that is most tender and sore, and which is usually referred to as giving a sensation of heat. If there are no special points of tenderness, the areas of most intense itching will serve as a guide to the underlying retention pockets.

The appearance of the diseased crypt varies with the degree of infection in the tissues. A recently diseased crypt may be bright red, older areas are purplish blue like a varicose scar, and still other ulcerated spots are reddish-brown or brown.

During the examination pus can often be demonstrated in the crypts, and not infrequently a sinus or a blind internal fistula will be found leading from a diseased crypt. These sinuses will vary in length from one-half to two inches (1 to 5 cm.) and extend usually in a radial direction from the crypts. The crypts are larger and of greater capacity than tonsillar crypts.

When foreign material becomes lodged in a crypt, it irritates and ulcerates the crypt wall thus initiating suppuration and absorption. It is with difficulty that any of these particles are dislodged, and they usually remain to traumatise and ulcerate the crypt. Anal cryptitis is probably the most frequently overlooked source of focal infection that is present in the human body today.

There is a type of rectal obstruction or really a constriction that has not been generally recognized. This constriction is due to a fibrosis of the pectin, doubtless caused by infection of the crypts. Most of these cases will admit the finger, though possibly with some discomfort. A more careful examination of the anal canal will show a constriction, not of the whole anal lining, but of only a very narrow band near its center. It feels much like a string tied around the anal canal. This condition must not be confused with the string-like constriction of scirrhus cancer of the rectum.

Some writers consider cryptitis a rare condition, but our experience reveals cryptitis more often than is suspected, and is the probable cause of more reflex disturbances than any other one rectal condition. It is seemingly, a minor affair, hence is often overlooked.

TREATMENT

Beginning or mild cases of cryptitis can be cured by making topical applications through a slanting anoscope. The feces must be kept soft and each diseased crypt thoroughly cleansed, by flushing with water, before any medicament is applied. A syringe with an angulated nozzle is essential to get to the bottom of the crypt. Dental syringes act very well.

After the crypt has been flushed clean, it may be bathed with 2 per cent solution of silver nitrate or

for more active stimulation, a probe dipped in pure ichthyol is passed in through the speculum and into the crypt. With great care the probe applies the ichthyol directly to the ulcerated area. This process is continued daily until all pain has disappeared, as can best be determined by passing a bent probe directly into the crypt.

CRYPTECTOMY

If there is much destruction of tissue and a burrowing process has begun, it is only wasted effort to make topical applications. A cryptectomy should be done at once. No general anesthetic is necessary as a local anesthetic acts well.

The preparation for the operation is as follows: He is given a sodium bicarbonate enema the night before operation and again the following morning. If he is nervous a preliminary hypodermic of morphine sulphate, one-fourth grain and scopolamine hydrobromide, one-hundredth grain is administered. He is placed on the operating table in the left Sims position, and the perineum, anus and buttocks are painted with one-half strength tincture of iodine which is then washed off with alcohol. The anesthetic solution is one-half per cent novocaine. A 10 cc. syringe fitted with a $2\frac{1}{2}$ inch long needle is used. The needle must be sharp, flexible and of fine caliber so that it can be curved easily. The lesser sphincter nerves are first blocked by inserting the needle one-half inch behind the posterior commissure, and then advancing it around the anal circumference, placing the solution beneath the skin. In three to five minutes the sphincter is completely relaxed, the anal canal and the lower rectum can be completely exposed by eversion by traction with triangular forceps, which are placed on the skin margin at the four points of the compass.

A blunt hook is now slipped into the crypt or channel, lifting the tissue toward the midline, or lumen of the anal canal, and with scissors, a triangular section, base upward, of the crypt is clipped off. This excised portion of the wall or "roof" of the crypt, transforms the crypt into an open groove. If there are any sinuses leading down from the diseased crypts, they should be excised. I do not content myself with splitting the crypt because the cut surfaces may remain to become a continual source of annoyance. The entire valve must be removed and the pocket completely obliterated. Bleeding sufficient to require ligation is rarely encountered. Of course any other indicated procedures, such as the removal of polyps, hemorrhoids, fistulas or fissures should be cared for at the same time. Care must be exercised during the operation not to over-distend the tissues; as the operating landmarks may thus be obliterated. If a sinus extends down into an external skin tab, the tab should be removed. Sometimes a sinus will extend a considerable distance out under the skin, and at some point in the raphe, either anterior or posterior, will be found the site of most intense itching, burning or pain, from which branch channels may lead to distant points.

The exquisitely tender or sensitive points are frequently the external evidences overlying sero-mucous sacculations and are vantage points for opening the subcutaneous channels. Such an area may be completely blocked off with additional infiltration of the anesthetic solution and opened down to the fatty

tissues. Quite a large cavity may be found here, filled with broken-down, blood stained or brownish-colored tissue. This tissue must all be removed with a curette and a search made for channels leading from this cavity. It is often surprising to find the probe slip along a considerable channel. Other channels may be found, extending out on the buttocks, sometimes encircling the anus or extending widely to the scrotum or thighs. After an opening has been effected into the diseased area, anterior and posterior to the anus, the channel may be laid open toward the anus or away from it, without severing more than a few fibers of the external sphincter.

AFTER TREATMENT

As soon as the patient is returned to his bed, if he is hospitalized, or before he leaves my office, if he is ambulatory, I introduce a suppository of Stramonium Ext., grs. $\frac{1}{2}$; Thymol iodide, grs. 2; Acetanilid, grs. 2; then cover the anus with a large gauze pad supported snugly with my own T bandage.

The action of the bowels is not interfered with. He is not given an opiate, except for pain. On the evening of the second day he is given one ounce of mineral oil, by mouth, and a similar dose night and morning thereafter, as needed to insure a soft non-irritating stool. If the bowels do not move on the third day, he is given, that evening, a level teaspoonful of compound licorice powder.

Each night and morning, beginning on the second day, the patient is given a warm sitz bath, to keep the external parts clean and to relieve local congestion. Every third day all granulating surfaces are cleansed with boric acid solution and, if granulation seem sluggish, they are touched with ten per cent silver nitrate solution.

If extensive channel formation has taken place, so that mucous reservoirs are formed in the tissues about the buttocks, a persistent flow of irritating mucus may continue to cause annoyance. Under such circumstances, further search must be made for mucous channels or sacculations, until all have been reached and destroyed. Irrigation can sometimes reach these channels through counter openings, thus avoiding the necessity of opening the channel its whole length. If a probe, introduced into a sinus, can be observed along its course until the point comes near the skin, it is well to make a counter opening at such point and irrigate the channel through and through. There are, usually, but one or two main sinuses, although numerous small branches may exist; but when the principal ones are treated, the smaller branches will cause no further trouble.

It is not necessary to confine the patient to bed after the cryptectomy as the operation causes very little inconvenience, usually but a slight soreness for a few days. However, a fortnight is usually required for the parts to heal completely.

Adenocarcinomatous Pedunculated Polyp of the Esophagus

Report of a Case

By

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ALTHOUGH polyps of the esophagus are extremely rare, they are perhaps the most common type of benign tumors of the esophagus. A carcinomatous pedunculated polyp is an unusual pathologic finding.

In a survey of over 20,000 gastro-intestinal roentgen studies, not a single instance of carcinomatous polyp was encountered. Among these cases, an instance of a benign polyp was observed in the upper esophagus. In a review of the available literature no reference or record has been found of a case of pedunculated adenocarcinoma occurring in the upper esophagus.

Polyps are usually single. They may be sessile or pedunculated and are more often found in the upper portion of the esophagus. Polypoid tumors may be benign or malignant, are usually found attached to the anterior wall, and are commonly seen behind the cricoid cartilage, however, they may occur in any portion of the esophagus. According to Stewart, esophageal polyps are usually pedunculated, which produce obstructive signs. Polyps of the esophagus are more commonly seen in late life.

Histologically, adenocarcinoma of the esophagus is more or less rare. When this variety is observed, it is usually seen in the lower end, extending up from

the cardia of the stomach, from which organ the growth arises. Mallory likewise pointed out that adenocarcinomata are less common than other forms of carcinoma, and when found are usually located at the lower end of the esophagus close to the cardiac orifice of the stomach. The finding of an adenocarcinoma in the upper portion of the esophagus is rare.

A case of an adenomatous pedunculated polyp occurring in the upper esophagus is herewith presented.

CASE REPORT

Y. B., male, aged 70, complained of difficulty in swallowing for three months. Liquids were swallowed with greater ease than solids, solids causing dysphagia. There was no vomiting. He complained of some loss of weight and weakness. Roentgenologic examination of the esophagus revealed considerable dilatation of the lumen of the upper esophagus, above the level of the sternal notch. A fairly large sized polyp, measuring about 15 mm. in diameter was observed floating in the dilated esophagus. The polyp was surrounded by air, which aided in clearly outlining the tumor mass. The tumor appeared to be movable, shifting with change of position. The dilated esophagus ended more or less abruptly and became narrowed below the point of obstruction. An irregular poorly defined shadow was observed, extending downward from the polyp for

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Abnormalities in Rectal Tone and Contraction in Paraplegia and Hemiplegia*

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EXPERIMENTAL studies of cats have shown that tone in the smooth muscle of the rectum is increased after decerebration (Langworthy and Rosenberg, 1939). The changes are evident after section of the brain stem just anterior to the optic colliculi, but become maximal following section between the optic and acoustic colliculi. When transection is carried below the vestibular nuclei in the medulla or further down into the spinal cord, the rectal muscle no longer responds to stretch stimuli and spontaneous contractions are not observed.

In earlier studies we showed that similar changes occur in vesical muscle after decerebration. It was concluded that tone in the smooth muscle of the bladder is controlled by reflex arcs involving the mid-brain. When the tonic mechanism is injured, a condition of "shock" develops and the muscle is no longer responsive to stretch stimuli.

It was obvious, at least in the case of the vesical muscle, that the cerebral cortex normally influences tone. Patients with injury of the cortico-efferent pathways on one or both sides complain of urgency, frequency and incontinence. The vesical muscle is hyperactive to stretch stimuli, accommodates only a small volume, and develops a forceful contraction which empties the bladder completely. The patient can no longer control these contractions voluntarily (Langworthy, Lewis and Dees, 1936).

The present paper reports a study of rectal muscle responses in patients with unilateral and bilateral injury of the pathways from the cerebral motor cortex.

METHODS

The exact technique of our procedure is described in detail in the previous paper and a diagram of the apparatus is shown. A rubber balloon approximately two and a half inches long which contained 30 cc. of air before stretching began was connected by means of thick walled rubber tubing to a U-shaped water manometer of 5 mm. bore. The other end of the manometer was attached to a tambour which recorded on a kymograph the changes of pressure within the balloon. The lubricated, uninflated balloon was inserted into the rectum well above the sphincters. By means of a luer syringe 20 cc. increments of air were instilled through a T tube. Air was prevented from escaping from the system by the use of a two way valve. The height of the column of water was noted immediately before and after the instillation of air.

This gave an indication of the relative changes of pressure occurring within the balloon. We recognize the fact that the pressure readings have no absolute values. Since the same manometer was utilized in all of our experiments, the pressure changes are directly comparable. Respiratory excursions were recorded by means of a blood pressure cuff placed around the chest and connected with a tambour. Time was marked in five second intervals.

The patient was allowed to lie on the side or on the abdomen. He was asked not to talk or move during the experiment.

In the previous paper we discussed the properties of a rubber balloon and its influence upon the tracing.

RECORDS OF RECTAL DISTENTION IN NORMAL INDIVIDUALS

As a control for our experiments a number of records were made from healthy individuals to determine the types of responses which may be considered normal. Persons were selected who had no complaints or findings suggestive of organic disease of the central nervous system.

The record made from the first patient is shown in Graph A, Fig. 1. Twenty-one increments of 20 cc. of air were introduced. With the first few additions the pressure rose rather rapidly; later distention did not produce as great an increase in intrarectal pressure. A contraction of the muscle in response to stretch can be seen in many places after the sudden distention of the balloon. The stretch responses are marked near the beginning and again near the end of the record. Respiratory waves are recorded in many portions of the graph. No waves of contraction of the rectal muscle are seen. The patient was not uncomfortable and he made no attempt to expel the balloon.

The second normal record shown in Graph B is included to demonstrate the regular appearance of stretch responses after the addition of each increment of air. These tended to increase in strength as filling progressed. The waves marked with an x were adventitious, due to the patient moving or talking. Toward the end of the record rhythmical contraction waves of the rectal muscle appeared.

In the third record (Graph C, Fig. 1) the rectal wall was relatively insensitive to stretch stimuli, and no waves of contraction are seen. Very small responses to stretch are observed. At the beginning of distention the wall showed an ability to accommodate the pressure and indeed the accommodation was good throughout filling.

The records made from normal individuals give us a standard to compare with the observations upon

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patients. The normal rectal wall often shows a response to sudden stretch produced by the addition of an increment of air to the balloon. These responses vary in individuals and would probably show similar changes in threshold in the same person under different circumstances.

BEHAVIOR OF THE RECTAL MUSCLE IN HEMIPLEGIA

Twenty-five patients with hemiplegia were studied; the following are representative cases:

Case 1. W. H. W., (V. A. H., 9593) was a white male of 61 years who developed a right hemiplegia. There was a right facial paralysis. Motor power was lost and tone increased in the right upper and lower extremities. The deep reflexes were hyperactive on this side. The abdominal reflexes were absent on the right, diminished on the left. Hoffmann and Babinski reflexes were present on the right. There was a right ankle clonus. A motor aphasia was present. The patient defecated regularly without the use of laxatives, and there was no bladder or rectal incontinence.

waves of contraction. At the end of the record a strong contraction occurred which expelled the balloon.

Case 3. M. C., (V. A. H., 9123) was a white male 43 years of age who had a cerebral vascular accident. As a result he developed right hemiplegia and motor aphasia. The Wassermann reaction was positive in the blood and spinal fluid. Examination revealed small irregular pupils which were fixed to light and accommodation. There was weakness of the facial muscles on the right. The muscles of the right arm were moderately atrophic. The fingers were tightly flexed. The patient could use his right leg, although it was a little weak. There was increased tone of both extremities. The deep reflexes of the right leg were moderately overactive, of the right arm markedly overactive. Hoffman and Babinski signs were present. The patient was incontinent of urine and feces.

Graph C in Fig. 2 is the record of rectal distention. Twelve increments of 20 cc. of air were introduced. The stretch responses increased in amplitude as distention continued. Rhythmical waves also appeared in the latter portion of the record. At the end a large contraction wave caused the balloon to be expelled.

Case 4. J. W. C., (V. A. H., 7204) was a white male, 51 years of age, who had a cerebral vascular accident

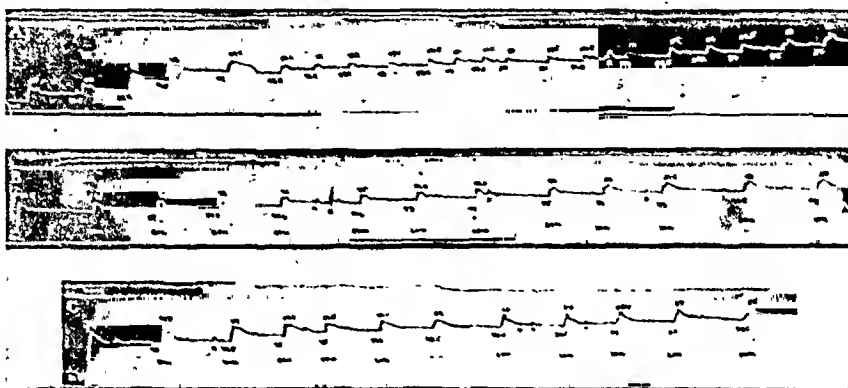


Fig. 1

The record from this patient is shown in Graph A, Fig. 2. The amplitude of respiration shows rhythmical variations. After six increments of 20 cc. of air had been introduced, marked stretch responses occurred in the rectal muscle. They produced peak-like waves which were of comparatively short duration. After the eighth increment was added the stretch response was very marked. Further peaks of contraction then occurred periodically, and tended to decrease in amplitude. Stretch responses also followed the addition of the ninth quantity of air. Another wave of contraction then expelled the balloon from the rectum.

Case 2. W. D., (B. C. H., 10393) was a white male of 66 years who lost the use of his right arm and leg following a sudden attack of unconsciousness. There was a concurrent aphasia. On examination it was noted that the right arm was flexed at the elbow and wrist, the right foot inverted and in a position of plantar flexion. There was increased tone in the paralyzed extremities and the deep reflexes were brisk. Hoffman and Babinski reflexes were present on the right.

The record of rectal distention in this case is shown in Graph B, Fig. 2. Again the rectal pressure was high during the early stages of distention. Fourteen increments of 20 cc. of air were introduced into the balloon. The stretch responses increased in strength and amplitude as filling progressed. There were also short unsustained

eight years ago, producing a right hemiplegia. The Wassermann reaction was positive in the blood. The spinal fluid findings were characteristic of meningo-vascular syphilis. The pupils were unequal, the left being larger; both were irregular and did not react to light or accommodation. There was paresis of the right side of the face. The tongue protruded slightly to the right. There was some weakness of motor power in the right arm. Tone was increased in the muscles of the right upper and lower extremities and the deep reflexes were overactive. The Hoffmann and Babinski signs were present on the right and there was an unsustained ankle clonus. He was incontinent of urine and occasionally of feces.

Graph D in Fig. 2 shows the effect of rectal distention. Twelve increments of 20 cc. of air were introduced into the balloon. The respiratory waves are registered upon the rectal record. As filling progressed the stretch responses increased in amplitude. After the twelfth addition of air a powerful wave of contraction pushed out the balloon.

BEHAVIOR OF THE RECTAL MUSCLE IN PATIENTS WITH BILATERAL INVOLVEMENT OF THE CORTICO-EFFERENT PATHWAYS

Twenty-four records were made from patients with bilateral involvement of the cortico-efferent pathways. These lesions usually produced paralysis of the limbs

upon both sides and signs of pseudobulbar palsy. Four representative cases are presented:

Case 5. F. S. H., (V. A. H., 8975) was a white male 56 years of age. As a result of a cerebral vascular accident he developed a right hemiplegia and aphasia. Three days before the rectal reading was made the patient had a convulsive seizure and lapsed into coma. He did not regain consciousness and died in five days. On neurological examination made the day of our present studies the pupils were dilated, equal, a little irregular, and fixed to light. There was immobility of the right side of the face. The tone of the right arm and leg was moderately increased and the deep reflexes on that side were brisk. The left extremities were flaccid and the deep reflexes only moder-

ately associated with urgency. He complained of difficulty in swallowing. There was emotional instability. The right pupil was larger than the left; they both reacted well to light and accommodation. The optic discs were pale and flat. There was marked horizontal nystagmus on looking to either side. The facial movements were stronger on the right. Speech was slurred and almost incomprehensible. The abnormalities of the extremities were more marked on the right side of the body. Decreased tone was present everywhere. There was ataxia of both arms. The legs were so weak that they could not be lifted from the bed. The deep reflexes in the arms were increased bilaterally. The knee jerks were present but no ankle jerks could be obtained. There were bilateral Babinski signs. The ab-

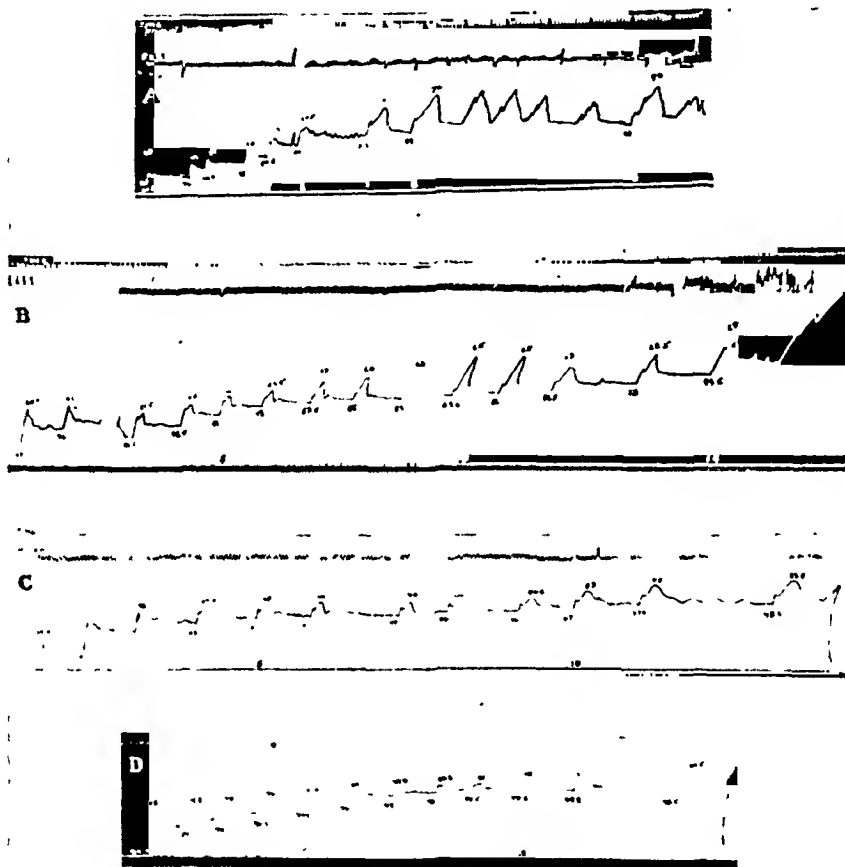


Fig. 2

ately active. The abdominal and cremasteric reflexes were absent. An ankle clonus was obtained on the right. The Hoffmann and Babinski signs were present bilaterally. There was loss of control of the bladder and rectum.

The record from this patient is shown in Graph A, Fig. 3. Respiratory waves are seen throughout the curve. The two groups of sharp, quick rises of pressure were due to the patient's coughing. Thirteen increments of air were introduced. No responses to stretch are seen in the record. At the end of filling two strong waves of rectal contraction occurred; the second extruded the balloon.

Case 6. J. S., (B. C. H., 31974) was a white male, 43 years of age who came to the hospital because he could not walk. There was frequent fecal and urinary incontin-

ence associated with urgency. Perception of passive movement was impaired in the toes; vibratory sensation was lost below the costal margins. The Wassermann reaction was negative in the blood and spinal fluid. The diagnosis of disseminated sclerosis was made.

The record from this patient is shown in Graph B of Fig. 3. Stretch responses appear after the addition of each increment of air. Toward the end of filling small rhythmic waves are evident. After the addition of the fourteenth increment a strong stretch response caused expulsion of the balloon.

Case 7. C. L., (B. C. H., 17804) a colored male of 43 years, came to the Baltimore City Hospitals because of increasing weakness and inability to walk. The present illness began at the age of 16 when a spinal deformity de-

veloped and a diagnosis of Pott's caries was made. Weakness and then paralysis of the legs developed. He was placed in a cast and function returned in the legs so that he was free from symptoms. Later the paralysis returned. He now showed a marked paraplegia. There was greatly increased tone in the legs. He could not walk because of loss of voluntary power. There was patellar and ankle clonus. Positive Babinski reflexes were elicited bilaterally. Below the hips there was loss of sensation of touch, vibration, and passive movement, and a decrease in pain perception. There was severe constipation. The diagnosis was spastic paraplegia secondary to tuberculosis of the thoracic vertebrae and compression of the cord.

The record from the patient appears as Graph C in Fig. 3. The initial pressures in the system were higher than normal. The respiratory waves are well recorded. Only

addition small rhythmical rectal waves. Stretch responses occur after the addition of increments of air. After the addition of the sixth increment, a strong contraction wave ejected the balloon.

SUMMARY

Graphic records showing the reactions of the rectal muscle to distention with air were made in normal individuals and in hemiplegic and paraplegic patients. The normal rectal wall often contracts in response to sudden stretch. These responses vary in different individuals and would probably show similar changes in threshold in the same person under different circumstances. In the patients with hemiplegia and paraplegia the response to stretch stimuli was much more active. There were also rhythmical waves of rectal

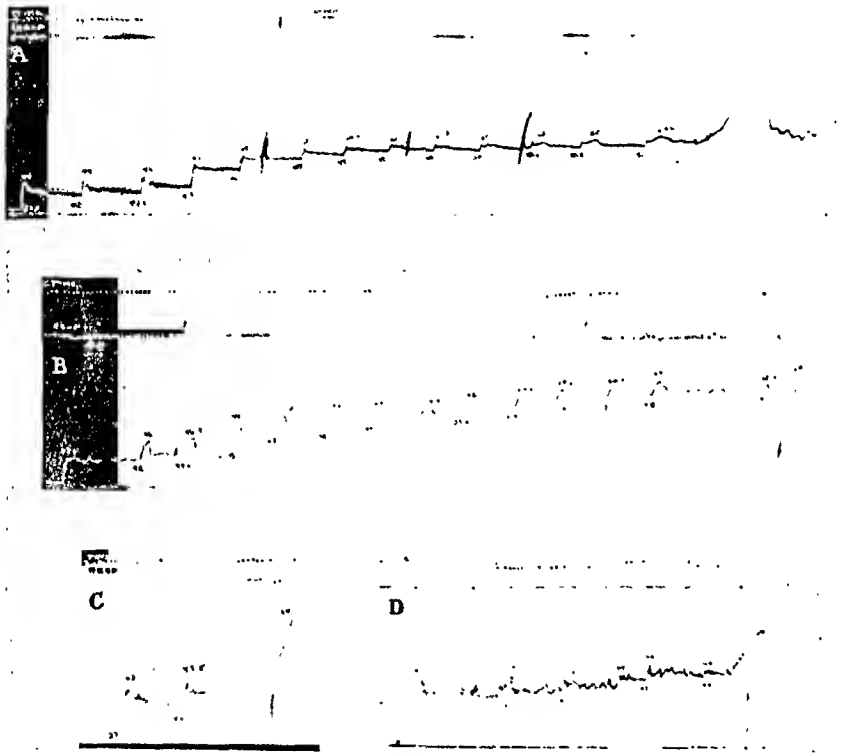


Fig. 3

three increments of 20 cc. of air could be added. The first two gave rise to no stretch response; after the third a strong contraction of the rectal wall expelled the balloon.

Case 8. J. W., (B. C. H., 11510) was a colored male of 69 years. He had noticed gradually increasing weakness of the arms and legs with stiffness of the legs four months prior to his admission to the hospital. There was atrophy of the intrinsic muscles of the hands. Motor power of all extremities was much diminished. Both legs were spastic with overactive deep reflexes and clonus. Fibrillations were visible in the scapular region. No sensory changes were observed. A diagnosis of amyotrophic lateral sclerosis was made.

The record from this patient is given in Graph D of Fig. 3. The respiratory waves are shown and there are in

contraction elicited by distention which became of sufficient strength to expel the balloon. The rectal wall was more resistant to distention than normal. These responses were in general more marked in individuals with bilateral injury of the corticospinal fibers. They suggest a release of tone in the smooth muscle of the rectum from normal control by the cerebral motor cortex.

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The Nutritional Availability of Iron in Molasses*

By

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INTRODUCTION

THE incidence of nutritional anemia in children, especially young children, is surprisingly high. Data are not yet adequate to allow the presentation of any figures which will truthfully indicate the prevalence of this type of disease, but numerous clinical tests show that the incidence may be as high as 70 per cent in a population group (1) and that the blood of less than 10 per cent of the individuals in this group is "normal."

Mackay has shown the nutritional importance of this disease by demonstrating that the incidence of colds, sore throats and pneumonia is halved by administering iron to anemic infants. Similar results are obtainable with foods containing significant quantities of available iron.

Nor is nutritional anemia confined to the young. In one typical investigation (2) 3500 persons were studied. It was found that 41 per cent of the infants, 32 per cent of the preschool children, 2 per cent of the school children, 16 per cent of the adolescent women, and 45 per cent of the adult women were definitely anemic. The blood of relatively few was definitely normal.

Nutritional anemia is to be found in all age groups and in all portions of our population. Severe cases are not uncommon and the number of individuals with subclinical hypochromic anemia is much larger than ordinarily supposed. This condition can be prevented by the ingestion of foods containing an abundance of readily available iron.

Molasses is one of the cheapest foods and is unusually rich in calcium and iron. Only one publication (3) has been found which reports on the "availability" of iron in molasses. It reports that the iron in "golden syrup" treacle is 95 per cent available and in black treacle is 100 per cent available. Both determinations were made by the dipyriddy (chemical) method. We have investigated the availability of iron in molasses further and are now reporting our findings.

There are essentially three methods by which the availability of iron in a preparation may be assayed: chemical, biological, and clinical. Previous to 1933 it had not been realized that there was need of such an assay, since it was not known that the nutritional value of food or medicinal iron is dependent upon its valence and upon the molecule in which it is contained.

In the chemical method an assumption is made that only the iron which under certain conditions (4) reacts with Hill's alpha-alpha dipyriddy reagent is nutritionally available. In the biological method, white rats are made anemic on a low-iron diet and the hemoglobin response of one group of animals to a measured

feeding of the food iron is compared with the hemoglobin response of a concurrent group of rats to the same amount of iron fed as ferric chloride or ferrous sulphate, compounds in which the iron is readily available.

In the clinical method, anemic infants or children are fed measured amounts of food iron and when the reticulocyte count has returned to a constant level, readily available iron (ferrous sulphate) is fed. If the continuation of the same amount of iron in inorganic "available" form produces a secondary rise in reticulocytes, it is assumed that the food iron is less available than the standard iron salt. By administering decreasing amounts of the medicinal iron to successive subjects a level is reached at which no secondary response follows. By comparing the amount of iron at this level with the amount of food iron it is possible to estimate the availability of the food iron relative to the medicinal iron.

The present paper presents the results of estimations of the availability of molasses iron as determined by the chemical (dipyriddy) procedure and by the biological assay procedure. A subsequent paper (5) will report the results of clinical assays on identical samples of molasses.

DESCRIPTION OF MOLASSES SAMPLES

The molasses used in these tests is prepared from Louisiana sugar cane. The juice is extracted by pressure from crushed cane, heated, treated with sulphur and lime to precipitate some of the impurities, clarified and concentrated to 40° Baume by heating at 63° F. This sugar cane syrup is boiled down still further to crystallize the sugar, and the resulting liquor is called a "First" Molasses—Sample A.

A portion of this "First" molasses is diluted with cane juice and reworked to obtain another extraction of sugar. The resulting liquor is called "Second" Molasses—Sample B.

The "Second" molasses is diluted with water, re-boiled to obtain another extraction of sugar and the resulting liquor is called "Third" Molasses—Sample C.

In the canning of the molasses used in these tests* the product was heated to 150° F. to "sterilize" and sealed so that the inside of the container was at reduced pressure.

AVAILABILITY OF MOLASSES IRON

I. CHEMICAL METHOD

The "available" iron in the three kinds of molasses was determined by the modified dipyriddy method (4). Blanks were used in making color comparisons as

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*The three grades of molasses used in these tests were produced by Panick and Ford, Ltd., Inc., and were purchased on the market.

suggested by Shackleton and McCance (3) because of the color contributed by the molasses. The total iron was determined on ashed molasses by the dipyrldyl method. Results of these estimations are given in Table I.

AVAILABILITY OF MOLASSES IRON II. BIOLOGICAL METHOD

Smith and Otis (6) have suggested methods by which the bioassay of the "available" iron in food-stuffs might be made. Following the procedure of Elvehjem et al (7) they rendered rats anemic by the use of a milk diet fortified with 0.05 mgs. of copper as copper sulphate, and 0.04 mgs. of manganese as manganese chloride daily. When the hemoglobin level

TABLE I
Summary of chemical estimations

Sample	Milligrams Iron/100 grams		"Availability"
	Total	"Available"	
A	3.2 ± 0.2	3.1 ± 0.1	97%
B	6.0 ± 0.5	5.1 ± 0.2	85%
C	11.3 ± 0.5	6.1 ± 0.3	54%

had dropped to 3.9 grams per 100 cc. of blood, a supplemental feeding of food or medicinal iron was made during a subsequent period of six weeks.

In the tests being reported, male albino rats of the Wistar strain (Sprague-Dawley) were transferred from a stock diet to an anemia-producing diet (8) of powdered, spray-dried whole milk (Klim). These animals were twenty-eight days old and weighed 50 to 60 grams on entering the test. They were individually housed in cages with false bottoms and supplied with water which had been twice-distilled in glass, and weighed twice weekly during the experimental period. A Sahli-hemoglobinometer was used in determining the hemoglobin content of the blood, which was obtained by cutting a caudal vein with a razor blade. In each case weekly determinations were made on 20 cmm. of blood. As recommended by Smith and Otis (6), 50 micrograms of copper as copper sulphate and 40 micrograms of manganese as manganese chloride were fed daily to each rat during the

entire depletion and test periods. The test period extended thirty-five days in every case.

The standard iron preparation used in this work was ferric chloride, U.S.P. Spectrographic analysis showed that this sample contained 20.50 per cent iron and 0.003 per cent copper. A pure preparation would contain 20.66 per cent iron and no copper.

The three samples of molasses used in this biological assay have already been identified. We added a fourth molasses to the study. Molasses A was fortified with ferric chloride so that half of the iron in each gram of fortified molasses was molasses-iron and half ferric chloride iron.

Series I: In the first series 0.15 milligrams of iron were fed to successive groups of rats in the form of ferric chloride or molasses. The ferric chloride was fed by mixing the pulverized sample in the powdered milk diet. The molasses was diluted with glass-distilled water so that daily feedings of 10 cc. portions could be pipetted into the feeding jars and was fed separate from the diet.

Space does not permit the presentation of the data on each animal. The data of each group of twelve animals have been averaged and are presented in Table II.

The availability of the iron in Molasses A appears to be less than that of the standard iron, but more than that of both Molasses B and C. Since the hemoglobin response is not linear, it is not possible to calculate the per cent availability of the molasses iron from these data. As might be expected, the results with Molasses A fortified with ferric chloride were excellent. The hemoglobin response of the animals fed this molasses was nearly identical to that of the rats fed ferric chloride.

Series II: A more accurate procedure for the determination of the availability of food iron is to vary the feeding level of the food or of the medicinal iron until the same degree of hemoglobin response is produced in the standard and the test group of animals. We have, therefore, varied the amounts of Molasses A and Molasses B fed successive groups of rats and compared the results with those produced by 0.15 milligrams of ferric chloride iron daily. The experimental procedure was precisely the same as in the previous series. The results are given in Table III.

The results of these tests indicate that 0.167 milligrams of iron in Molasses A were more than equivalent

TABLE II
Summary of biological assay data, Series I

Rat Numbers	Supplement	Grams Supplement Per Day	Milligrams Iron in Supplement Per Day	Weight in Grams			Hemoglobin (gms./100 cc.)		
				Initial	Cleared	Final	Cleared	Final	Change
18500-11	none			54	111	174	3.2	2.7	-0.5
18512-23	ferric chloride	.000729	0.15	54	113	185	3.1	7.6	+4.5
18524-35	Molasses A	3.571	0.15	54	120	229	3.2	6.6	+3.4
18536-47	Molasses B	2.344	0.15	54	116	210	3.2	5.7	+2.5
18548-59	Molasses C	1.351	0.15	54	116	199	3.2	5.9	+2.7
18560-71	Molasses A ferric chloride	.000364	0.15	53	112	206	3.2	7.4	+4.2

Spectrographic analysis: Molasses A 0.0042% Fe; Molasses B 0.0054% Fe; Molasses C 0.0111% Fe; Ferric chloride 20.50% Fe.

TABLE III
Summary of biological assay data, Series II

Rat Numbers	Supplement	Grams Supplement Per Day	Milligrams Iron in Supplement Per Day	Weight in Grams			Hemoglobin (gms./100 cc.)		
				Initial	Cleared	Final	Cleared	Final	Change
21290-93	none			54	168	185	4.0	2.8	-1.2
21250-59	ferrie chloride	.000729	0.15	55	156	178	3.5	7.3	+3.8
21260-69	Molasses A	5.33	0.167	54	165	199	3.7	7.7	+4.0
21270-79	Molasses A	6.054	0.188	54	160	199	4.0	8.5	+4.5
21280-89	Molasses A	6.910	0.214	54	151	195	3.7	8.5	+4.7
20104-13	none			54	175	227	3.6	2.7	-0.9
20060-70	ferrie chloride	.000729	0.15	55	181	215	3.4	7.2	+3.8
20071-81	Molasses B	2.45	0.167	54	165	199	3.7	7.7	+4.0
20082-92	Molasses B	2.76	0.188	56	197	245	3.4	7.2	+3.8
20093-103	Molasses B	3.15	0.214	55	187	237	3.5	7.7	+4.2

Spectrographic analysis: Molasses A 0.0031% Fe, 0.00135% Cu; Molasses B 0.0068% Fe, 0.0019% Cu; Ferrie chloride 20.50% Fe, 0.003% Cu.

lent to 0.15 milligrams of ferrie chloride iron. Its availability is, therefore, at least 90 per cent that of the iron of ferrie chloride. That it is less than 100 per cent as available was indicated by the results of Series I.

Similarly, 0.188 milligrams of iron in Molasses B were equivalent to 0.15 milligrams of iron as ferrie chloride. The iron of Molasses B was therefore approximately 80 per cent as available as that of ferrie chloride.

DISCUSSION

Although the iron in high-grade molasses is more available than that in a lower grade of molasses, the

higher grade is not as rich in total available iron. For example, 100 grams of Molasses A furnished slightly more than 3.1 milligrams of "available" iron, whereas the same quantity of Molasses B contained approximately 5.1 milligrams of "available" iron.

The results obtained with Molasses C do not agree with Shackleton and McCance (3) who reported that the iron in black treacle is 100 per cent available. In our experience only 54 per cent was available.

It is not correct to base one's judgment of a food on its total iron content since iron availability varies with the kind of food. This is demonstrated in Table IV where the total and available iron content of important iron-rich foods is presented. The values for total iron were taken from Sherman (10) and the availability of the iron from two sources (3, 9). At the top of the table we have listed the data on the three molasses which are the subject of this publication. We have assigned an availability of 85 per cent, in accordance with our findings on Molasses B, to the molasses in Sherman's table because the total iron content is relatively the same and Molasses B is the type commonly used in the home.

It is apparent from this table that of the foods reputed to be excellent sources of iron, only liver compares favorably with molasses. Whipple and Robschert-Robbins (11) have listed chicken and beef liver, chicken gizzard, beef kidney, eggs, apricots and raisins as especially valuable in the cure of anemia. It appears, however, that molasses is superior to all of these foods in this respect and is, moreover, the most inexpensive food source of iron.

SUMMARY

1. The availability of the iron of three grades of molasses ("first," "second" and "third") has been determined by chemical (dipyridyl) and biological procedures.

2. By the chemical procedure the "availability" was found to be 97 per cent, 85 per cent and 54 per cent, respectively.

3. By the biological (rat) method the availability

TABLE IV

	Total Iron* mg./100 gm.	Per Cent Availability	Available Iron mg./100 gm.
Molasses "C"	11.3	54	6.1
Molasses "B"	6.0	85	5.1
Molasses "A"	3.2	97	3.1
Molasses	7.3	85	6.2
Beef liver	8.2	70	5.6
Oatmeal	4.8	96	4.6
Apricots (dry)	4.1	98	4.0
Eggs	3.1	100	3.1
Wheat	5.0	47	2.4
Raisins (Muscat)	3.0	62	1.9
Parsley	3.2	50	1.6
Beef muscle	3.0	50	1.5
Oysters	5.8	22	1.3
Cabbage	1.8	72	1.3
Mutton	5.1	24	1.2
Lettuce	1.5	63	0.9
Spinach	2.6	20	0.5

*Total iron values have been taken from Sherman's "Chemistry of Food and Nutrition," 1937.

Per cent availability values have been taken from Sherman, Elvehjem and Hart (9), Shackleton and McCance (3), or this paper.

was slightly over 90 per cent, approximately 80 per cent, and 50 per cent, respectively.

4. The dipyriddy procedure is acceptable for the

determination of the availability of iron in molasses.

5. Molasses is a rich and inexpensive source of available iron.

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A New Approach to the Prevention of Hemorrhages from Esophageal Varices as Occur in Cirrhosis and Banti's Disease*

By

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MOST investigation of Banti's disease and primary cirrhosis of the liver has been directed toward discovery of the etiology of these diseases. Although this goal has not been attained, much has been added to our knowledge of the pathological anatomy and physiology of the two entities. As a result of this knowledge certain therapeutic procedures have been instituted with variable results. It is my purpose to describe herein another form of treatment to be used in those cases in which hemorrhages continue following unsuccessful use of accepted therapeutic procedures. It will be well to review the pathological physiology of the portal system, the therapeutic procedures already in use and the hydrodynamics of the flow of a liquid through small tubes.

In Banti's disease and in primary cirrhosis of the liver there exists an increased resistance to the flow of blood through the liver. This results in an increased pressure in the portal vein, commonly termed portal hypertension. There can be little doubt about the increased resistance to blood flow through the liver. The fact that blood takes new channels (collateral circulation) on its way back to the heart from the portal vein is in itself sufficient proof. In addition, Caughey (1) has found that by actually testing the pressure in the portal vein in cases of hepatosplenomegaly there is a definite rise above normal. It seems logical that the primary cause of the increased resistance to blood flow through the liver is due to a narrowing of the caliber of the vessels. It was formerly believed that such narrowing was due to the constriction of surrounding cicatricial tissue in the portal lobule. However, Rousselot (2) and McMichael (3) questioned this, inasmuch as they repeatedly saw cases in which portal hypertension existed without gross changes in the liver. In these cases, however, biopsies were not done and it is conceivable that sufficient microscopic cirrhosis could exist to cause mechanical interference to the flow of blood in the small portal

vessels. The finding of microscopic cirrhosis without much gross evidence of liver damage has occurred in my own experience and in the experience of others. As a result of this portal dam, the collateral veins (4) are called upon to carry the excess load of venous blood to the heart. The veins of the esophagus dilate and hypertrophy as a consequence of this new load and if the burden is in excess, stretching of the vein to the point of rupture and hemorrhage takes place.

Several surgical procedures have been carried out in an attempt to alleviate the disastrous end results of portal congestion.

1. Splenectomy accomplishes three purposes. It diminishes the total blood volume entering the portal system by probably 25 per cent. It eliminates the factor of resistance of blood flow through the spleen. It eliminates the "toxic byproducts" of a diseased spleen.

2. The omentopexy operation is an attempt at establishing new venous connections between the portal circulation and the systemic circulation.

3. The ligation of the coronary veins of the stomach is an attempt to eliminate the channel of collateral circulation through the esophageal veins which are so vulnerable to rupture when overburdened.

4. Other procedures such as the Eck fistula, the anastomosis of the inferior mesenteric vein to the inferior vena cava, the canterization of esophageal varices, and the injection of esophageal varices with sclerosing agents have been found impractical.

The procedures of omentopexy, splenectomy and ligation of the coronary (gastric) veins are recommended, either singly or in combined form in all cases where the surgical risk is not too great. However, a successful end result is not always obtained. It has been noted that once hemorrhages occur from esophageal varices the probability of preventing hemorrhages by surgical procedures is diminished from 50 to 65 per cent (5). In other words, in slightly over one-half the cases of portal hypertension with hemorrhage from esophageal varices, the disease has ad-

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vanced to such an extent that failure to relieve symptoms results.

Obviously the primary difficulty is increased resistance of blood flow through the liver. In order to understand the factors concerned in blood flow through small tubes it is well to review Poiseuille's law in its formula arrangement (6). It can be set down as follows.

$$\frac{V}{t} = \frac{Q^2 (p-p')}{8 \pi N L} = \frac{r^4 \pi (p-p')}{8 N L} \\ \text{or transposed } (p-p') = \frac{8 N L V t}{\pi r^4}$$

Where V/t is the volume following in unit time, $p-p'$ is the pressure fall, Q is the cross-sectional area of the

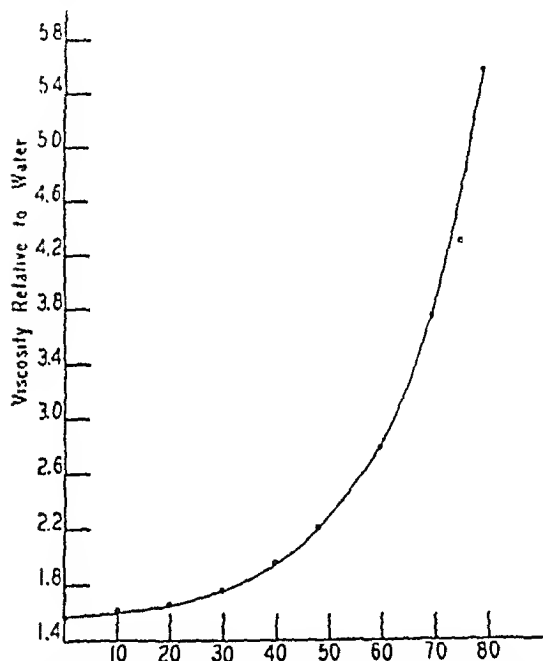


Fig. 1. The effective viscosity of blood relative to water (ordinates) compared with the concentration (percentage volume) of corpuscles in the blood (abscissae). The values were determined by perfusion of the isolated leg of a dog. (Data of Whittaker and Winton: *J. Physiol.*, 78:339, 1933). Reprinted by permission of C. V. Mosby Co.

vessel, r is its radius, L is the length, N is the viscosity of the fluid. According to this law three factors exist in the causation of "back tension" or pressure fall, namely, (1) the factor of length and radius of the vessel, (2) blood (fluid) volume, and (3) viscosity of blood (fluid).

The first factor, size of the vessel, cannot be altered in the case of a cirrhotic liver by any known means. The second factor, blood volume, can be altered by omentopexy and splenectomy. If this is insufficient the third factor, blood viscosity, can be altered by venesection. For all practical purposes blood viscosity depends on the ratio of cell count to plasma content. The higher the cell count the more viscid is the blood. This follows a definite curve (6) (Fig. 1). It will be noticed that the viscosity of blood increases slowly until the corpuscle concentration of 50 per cent is

reached. From that point, the viscosity climbs rapidly. Clinically, this observation is important. It has been repeatedly observed that a patient with hemorrhage from varices seldom completely recovers a normal blood count. Hemorrhages occur too soon. For purposes of convenience in description, the blood count level at which a patient will have a hemorrhage from an esophageal varix will be called the hemorrhage threshold. The hemorrhage threshold is reached when the blood viscosity is such that the flow of blood through the liver is hindered and the collaterals cannot withstand the excess load placed upon them. According to Poiseuille's law, this level would vary in different patients but should be more or less constant in any individual case. In the case to be cited this hemorrhage threshold was found to be at a hemoglobin of 60 per cent and an erythrocyte count of 4,100,000. This varied only within the accepted percentage of error of blood counting. The patient was watched for approximately six months and it was noticed that hemorrhages occurred at the above mentioned hemorrhage threshold. The hemorrhages occurred at intervals of eight to twelve weeks, depending upon the rapidity of new blood formation and the amount of blood lost. After this period of observation it was decided that a venesection of 400 cc. of blood would be done when the blood level reached a hemoglobin of 50 to 55 per cent and an erythrocyte level of 3,800,000 to 4,000,000. This proved to be successful, the blood viscosity being lowered sufficiently to allow for an adequate increase in circulation through the liver, and accordingly decreasing the load on the collateral circulation.

During the three years of this treatment the patient has been allowed to go without venesection on two occasions, once two years ago and once recently. It was observed that spontaneous hemorrhages occurred when the blood count reached the original hemorrhage threshold. At no other time has there been a hemorrhage since the onset of the treatment three years ago. This hemorrhage threshold should vary with different patients. It is conceivable that if more liver damage exists the hemorrhage threshold would be at a lower blood level. Likewise, the contrary would be true. The threshold level can be determined by counting the blood of known varix patients at weekly intervals and observing the level of the blood count at which hemorrhage occurs. The amount of blood to be withdrawn at the time of venesection depends upon the blood regenerative power of the patient. I believe in most cases of Banti's disease that the maximum should be 400 cc. at one time. In the case herein reported 400 cc. were withdrawn at intervals of six to eight weeks. Perhaps in other cases, where the blood regenerative power is slower, a 200 cc. venesection may be sufficient for that interval. This blood may be used for immediate transfusion if suitable in type or it may be given to a blood bank. The value of the procedure for controlling the viscosity of blood by venesection cannot be minimized. In the past a clinician handling these patients could not but be deeply impressed by their nervous anxiety. These patients could not leave home for fear an esophageal hemorrhage would occur while away. They lived in fear of a fatal hemorrhage. Also, during an esophageal hemorrhage there is a certain amount of physical discomfort resulting from nausea, vomiting, air hunger, gaseous

distension of the abdomen and weakness. Likewise, in repeated profound hemorrhages certain irreversible changes may take place such as fatty degeneration of the heart, liver and kidneys.

In addition to the prevention of hemorrhages, an attempt should be made to conserve the liver and the hematopoietic system in general by the administration of a high carbohydrate diet, injections of 10 per cent glucose in saline intravenously, liver extract intramuscularly at intervals, and vitamine concentrates. In the light of our present knowledge, this should be

which showed a mild secondary anemia. In 1932, the patient noticed tar-colored stools. At that time he entered a clinic (elsewhere) for the examination. Following the examination a diagnosis of Banti's disease was made. Esophageal varices were demonstrated both by X-ray and esophagoscopy. The intravenous bromsulphalein liver function test was positive. Shortly after the examination an omentopexy and ligation of the coronary veins of the stomach was done (elsewhere). It was noted that the liver appeared moderately cirrhotic. Following the operation, the patient developed ascites and hydrothorax which

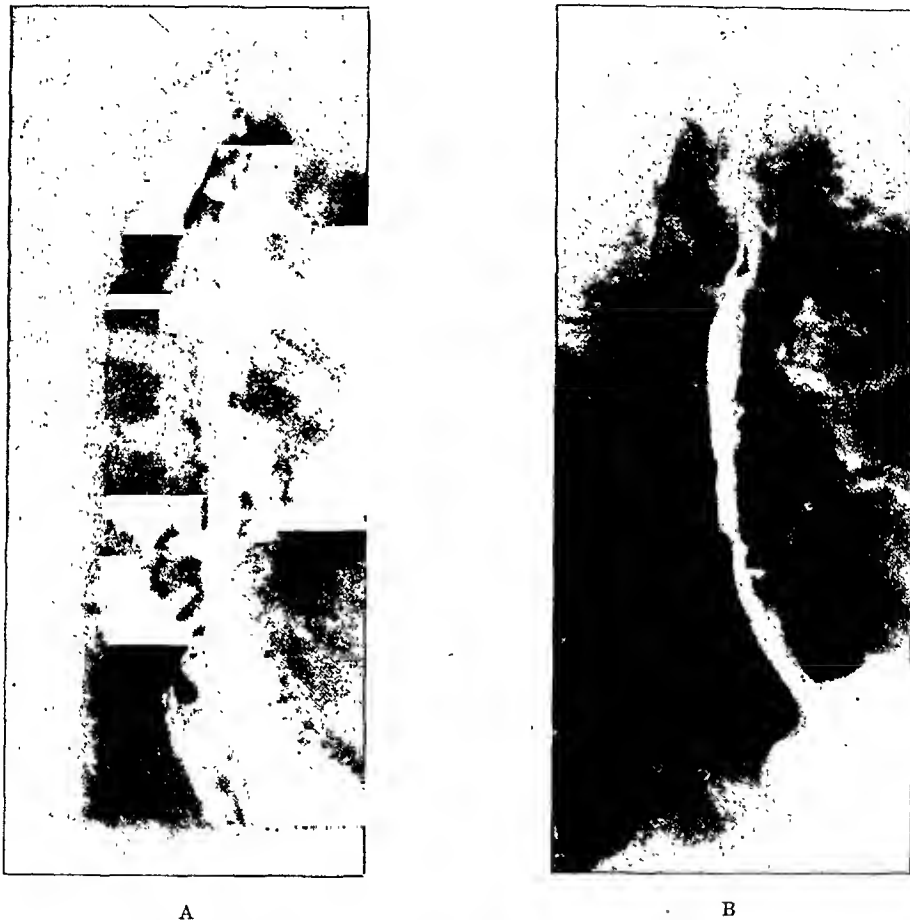


Fig. 2. A. The dilated state of the esophageal varices as the blood count nears the hemorrhage threshold. B. The collapsed state of the esophageal varices after venesection.

helpful as a prophylactic measure against further degeneration of the liver and against the possible further injury to the hematopoietic system. In the three years of observation on this form of treatment, there has been no evidence of change in the status of the liver nor has there been any evidence of slowing in the regenerative powers of the blood forming organs.

CASE REPORT

In the Fall of 1931 at the age of 51, the patient, a physician, first noticed that "something was wrong." There was a pallor of the skin and the hemoglobin was 65 per cent. At quarterly intervals a blood count was obtained

lasted six weeks. He continued to have esophageal hemorrhages varying at intervals of two to three months.

On September 22, 1935, he registered at the Carle Hospital Clinic complaining of vomiting blood following a severe paroxysm of coughing. The examination showed a pallor of the skin. The blood pressure was 130 systolic and 75 diastolic, the pulse 80 and the temperature 99.4°. The throat, heart and lungs were negative. The spleen was enlarged and extended three fingers' breadth below the costal margin. The liver edge could not be palpated. There was no evidence of enlargement of the superficial veins of the abdomen or thorax. There were no hemorrhoids. The patient was placed at rest, using a high carbohydrate liquid diet. After one week he was allowed to

be up and about. Thereafter, it was observed that at intervals of eight to twelve weeks he would have hemorrhages from the varices. It was also noticed that these hemorrhages always occurred when the hemoglobin reached a figure of 55 to 60 per cent and the red blood cells numbered approximately 4,000,000. It was decided that a splenectomy was indicated. Accordingly, this was performed elsewhere on February 11, 1936. The spleen weighed about 1500 gm. and the surgical pathological diagnosis was Banti's disease.

The convalescence was uneventful. As was expected following the operation, the platelet count arose to high figures. The patient returned home on March 7. On March 20, the hemoglobin was 58 per cent, the red blood 4,100,000 and the platelet count had dropped by this time to 150,000. On March 23, the patient had a hemorrhage. Prior to this, the hemorrhages would stop spontaneously after the hemoglobin reached a level of 30 to 40 per cent. In this instance, however, the blood platelets were lower than normal and the hemorrhage continued to the point of almost complete exsanguination. The patient was admitted to the Carle Memorial Hospital shortly after the onset of the hemorrhage. The patient became comatose as the hemorrhage continued. Eight transfusions of 500 to 600 cc. each were given within the next 48 hours. At the end of this time the hemorrhage had ceased. The hemoglobin content was 20 per cent and the red blood count was 2,230,000. On March 28, the platelet count had returned to normal (260,000). On April 14, the patient was dismissed from the hospital having a hemoglobin of 36 per cent, red blood count 2,830,000 and platelet count 280,000.

At this point it was decided that he should have "controlled hemorrhage" and accordingly the blood count was taken at weekly intervals. When the hemoglobin reached a level of 50 per cent or just above, a venesection of 400 cc. of blood was done. The procedure lowered the viscosity from a figure of 5.4 to one of 4.3 using water as 1.0. It was found that venesection became necessary every six to eight weeks. In addition, he received 500 cc. of 10 per cent glucose in saline intravenously and 1 cc. of concentrated liver extract intramuscularly, both at weekly intervals. After the patient had been on this form of treatment for six months an X-ray of the esophagus before and after venesection showed a decrease in the size of the varices after venesection (Fig. 2). Although it is generally conceded that the X-ray findings in esophageal varices are rather inconstant, the difference was so striking in this case that they are shown here. At that time it was decided to allow the patient to go without venesection. On November 24, the blood count showed a hemoglobin of 57 per cent and a red blood count of 3,990,000. According to our previous observations the patient was due for a hemorrhage. On December 3, he vomited blood and had

tarry stools. The blood count dropped until the hemoglobin was 41 per cent and the red blood count was 2,870,000. Periodic venesections were again resorted to whenever the hemoglobin arose to 50 per cent.

After three years of treatment along these lines the patient shows no evidence of tendencies to further injury to the hematopoietic system as shown by regular regeneration at intervals. The bromsulphalein liver function test which was positive before the omentopexy became negative after omentopexy and has remained so. Blood regeneration of 400 cc. continues to take place at regular intervals of six to eight weeks. In this case as in most cases of Banti's disease a hypochromic anemia exists as a result of an ill defined injury to the hematopoietic system. This is part of the syndrome of Banti's disease. As far as our knowledge is concerned this tendency to hypochromic anemia is fortunate inasmuch as many more venesections would be required to maintain the blood count at a lower level. In primary cirrhosis of the liver the blood regenerative powers are usually much greater than in Banti's disease and it is highly probable that venesection would have to be performed more often or in larger amounts or both in order to avoid esophageal hemorrhages.

SUMMARY

A form of treatment is suggested for use in patients who have hemorrhage from esophageal varices. The treatment consists of lowering the blood viscosity by venesection when the patient's blood count nears the predetermined hemorrhage threshold for that individual case. Lowering the blood viscosity increases the circulation through the liver and thus diminishes the burden on the collateral circulation. It is recommended that this form of treatment be used only in those cases where hemorrhages continue to occur after accepted surgical operations have been performed or on those cases where the risk of operation is too great.

In preventing esophageal hemorrhages from occurring by lowering the blood viscosity, certain definite accomplishments result, namely, (1) spontaneous hemorrhage is prevented, (2) the amount of blood loss is a known quantity by venesection and can be regulated, whereas, in spontaneous hemorrhage it may be of such an amount as to cause death, (3) the blood withdrawn by venesection can be used for transfusions, whereas, in spontaneous hemorrhage it is lost, (4) the physical and mental discomfort of a spontaneous hemorrhage is eliminated, and (5) general health is improved when the blood count is kept at a more nearly constant level.

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The Significance of the Presence of Calcium Bilirubin Pigment and Cholesterol Crystals in the Feces*

By

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EXAMINATION of stones removed from the gall bladder or bile ducts at the time of operation reveals that a high percentage are of three main types: calcium bilirubinate, so-called pure pigment stones; cholesterol stones; and mixed stones containing varying proportions of calcium bilirubinate and cholesterol. Other substances such as carbonates and phosphates may occur in varying combinations with calcium bilirubinate and cholesterol.

In cases in which the X-ray diagnosis is positive, the diagnosis of cholelithiasis offers little difficulty to the clinician. However, in those cases in which the X-ray evidence is equivocal additional diagnostic aids are required.

In 1931 H. L. Bockus et al (1) reported studies on the diagnostic value of the Lyon method of non-surgical biliary drainage in gall stone disease, calling attention to the previous studies by Piersol, Bockus and Shay (2), Hollander (3), Mateer and Henderson (4), Einhorn (5) and Jones (6). At that time Bockus reported that the finding of both calcium bilirubinate and cholesterol crystals in the bile drainage was pathognomonic of cholelithiasis. Bockus further reported operative confirmation of the presence of stones in 89 per cent of his cases in which cholesterol crystals alone were found in the bile drainage. Similar confirmation was reported in 90 per cent of his cases in which calcium bilirubinate alone was found in the bile drainage.

Thus, while a certain percentage of error obtains in the interpretation of the finding of calcium bilirubinate and cholesterol in the bile drainage, the method possesses distinct value.

If bile, removed from the upper intestinal tract by the Lyon technic, contains sufficient pigment and crystals to be of diagnostic importance in connection with gall stones, it is not unreasonable to believe that similar findings in the feces might be of value. However, apart from the factors that make for error in the interpretation of the presence of crystals and pigment in the bile drainage, one must not overlook a possible error in the feces examination due to intestinal changes which might tend to precipitate either calcium bilirubinate or cholesterol or both from the bile which was free from precipitation as it flowed into the duodenum from the common bile duct. The scope of the present report precludes a detailed consideration of the chemical changes in the bile that might occur in the lower intestinal tract.

The occasional presence of calcium bilirubinate, cholesterol or both in routine feces examinations led to the present study. Over an approximate three year period, 2003 stools were examined, in 67 of which calcium bilirubinate, cholesterol crystals or both were found. In many instances the stools came from patients who were in the hospital for study of some condition unrelated to the biliary tract. Table I represents a summary of our results.

DISCUSSION

In reference to the group in which calcium bilirubinate alone was found in the feces, excluding unstudied and doubtful cases, cholelithiasis was confirmed in 18 (72 per cent) of the remaining 25 cases. There were

TABLE I

Summary of the 67 instances in 51 cases in which calcium bilirubinate pigment, cholesterol crystals or both were found in the feces examination

	Cases	Cholelithiasis			
		(1) Confirmed	(2) Not Confirmed	(3) Doubtful	(4) Not Studied
Pigment	34	18	7	2	7
Crystals	14	1	6	0	7
Both	3	0	0	2	1
Total	51	19	13	4	15

- (1) Cholelithiasis: i.e., operation, necropsy, positive flat plate of abdomen, or demonstration of stones by the Graham X-ray study.
- (2) Cholelithiasis not confirmed: i.e., normal Graham X-ray study, operation in which inspection of the gall bladder failed to reveal cholelithiasis, or negative necropsy findings.
- (3) Cholelithiasis doubtful: i.e., non-functioning gall bladder by Graham test but stones not demonstrated on the plates, patient not operated upon, or crystals and pigment found in the bile drainage but no X-ray or operative confirmation.
- (4) Patient not studied: i.e., patient in the hospital for some condition unrelated to the gall bladder and the gall bladder was not investigated.

seven cases in which the diagnosis of cholelithiasis was not substantiated.

Apart from cholelithiasis, two mechanisms may account for the presence of calcium bilirubin pigment in the bile and consequently in the feces:

1. Sudden release of noncalculus mechanical block of the main bile ducts, such as might result from compression of the ampulla of Vater by edema or inflammation of the head of the pancreas. In one of our cases lymphosarcomatous infiltration of the adjacent structures undoubtedly was responsible for the common duct obstruction since a prompt recession of the jaundice followed epigastric irradiation and the

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roentgenologist reported a marked decrease in the size of the previously widened duodenal sweep.

2. An increase in the serum bilirubin secondary to increased hemolysis may give rise to calcium bilirubinate in the bile in the absence of biliary pathology. That mechanism is suggested in two of our cases, i.e. primary pernicious anemia, and Case 21, an acute hemoclastic crisis of a sickle cell anemia.

Of the seven cases in which the diagnosis of cholelithiasis was not confirmed there remain three cases in which the feces calcium bilirubinate pigment could not be explained, i.e., one case of typhoid fever and two cases of duodenal ulcer.

In a number of instances in the present series, the first intimation of possible gall stone disease was the finding of calcium bilirubin pigment in the feces of a patient in whom that diagnosis was not suspected.

It is not without purpose to urge that the examiner be thoroughly familiar with the microscopic appearance of calcium bilirubinate pigment. Typical pigment is so characteristic in appearance that there is little excuse for confusing it with the vegetable pigments that are commonly present in the feces. Questionable pigment or indeterminate microscopic appearances never should be reported. Typical cholesterol crystals are so characteristic that there is even less excuse for error in their identification.

Of 14 cases in which cholesterol crystals alone were reported in the feces, there was only one case in which the diagnosis of cholelithiasis was confirmed. Seven of the cases, however, were not studied for cholelithiasis.

There were only 3 instances in which both crystals and pigment were reported in the stools. One case was not studied for cholelithiasis and in two cases the findings were doubtful.

CONCLUSION

The presence of calcium bilirubin pigment in the stool should suggest further study of the patient to rule out cholelithiasis. The above findings are being reported in the hope that some more definite appraisal may ensue from study of larger groups of cases.

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The Physiological Control of the Normal Human Gastric Secretory Curve*

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BEFORE physicians can hope to prevent or modify various anomalies of gastric secretion they must know all of the factors controlling it. At the present time considerably more is known about the various mechanisms which initiate and maintain the secretion of acid than about the factors which inhibit acid secretion and regulate the gastric secretory curve.

In previously reported studies on animals (1, 2, 3, 4) it was shown that there are at least two mechanisms which are of great importance in regulating the gastric secretory curve, namely "acid inhibition" and duodenal regurgitation.

Acid inhibition controls the amount of acid secreted and functions as follows: As the acidity of the gastric contents increases a certain threshold value is finally reached at which the rate of acid secretion is greatly reduced, or in some instances almost completely inhibited. As the rate of acid secretion is reduced there is no reduction in the *strength* of the *pure acid secretion*; it is simply reduced in *amount*. Acid inhibition controls primarily the acidity of the gastric contents (cc. of acid secretion per 100 cc. of gastric contents). It is quite independent of duodenal regurgitation and can keep the acidity of the gastric contents within normal limits even in the complete absence of duodenal regurgitation (4).

Duodenal regurgitation becomes most pronounced near the end of the gastric secretory curve and results in the entrance of non-acid duodenal secretions into the stomach. By dilution and neutralization (primarily the former) the duodenal secretions lower the acidity of the total secretions which enter the stomach. Duodenal regurgitation always results in a lowering of the acidity of the *total secretions* entering the stomach below the value attained before duodenal regurgitation begins. Its effect upon the acidity of the *gastric contents* is variable and depends upon the relationship between the amount and acidity of the gastric contents, the rate of acid secretion and the amount of duodenal secretions regurgitated.

The present paper presents a study of the mechanisms of acid inhibition and duodenal regurgitation in the normal human subject.

ACID INHIBITION

(A) *Methods of Study*

In each subject the normal gastric secretory curve was first established by performing several experi-

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ments in which the standard aqueous (1) two per cent Liebig's extract test meal containing 15 mgm. of phenol red per liter was used as previously described (5, 6). Two per cent Liebig's extract meals with various acidity values were then used (2). Two types of experiments were performed as follows:

1. The standard meal contained from 18 to 24 cc. of N/10 acid per 100 cc., but for convenience it will be referred to as the aqueous meal.
2. In preparing the acid test meals a 4 per cent Liebig's extract meal containing 30 mgm. of phenol red per liter was first prepared and then mixed with an equal volume of an aqueous hydrochloric acid solution twice the strength of the final value desired. In calculating the strength of acid to be used in diluting the 4% meal, it was of course necessary to make due allowance for the acidity of the 4 per cent meal itself.

Type I. The fasting stomach was first thoroughly lavaged with 300 cc. of the acid meal to be used. After removal of the lavage 800 cc. of the acid meal were introduced by gravity as previously described (6). Every fifteen minutes until the stomach emptied the contents were thoroughly mixed and a sample (35 cc.) removed.

Type II. In the majority of experiments the stomach was first stimulated by using the two per cent aqueous test meal. After the secretion of acid had reached a high rate, the aqueous meal was removed and the acid meal introduced. This type of experiment is much

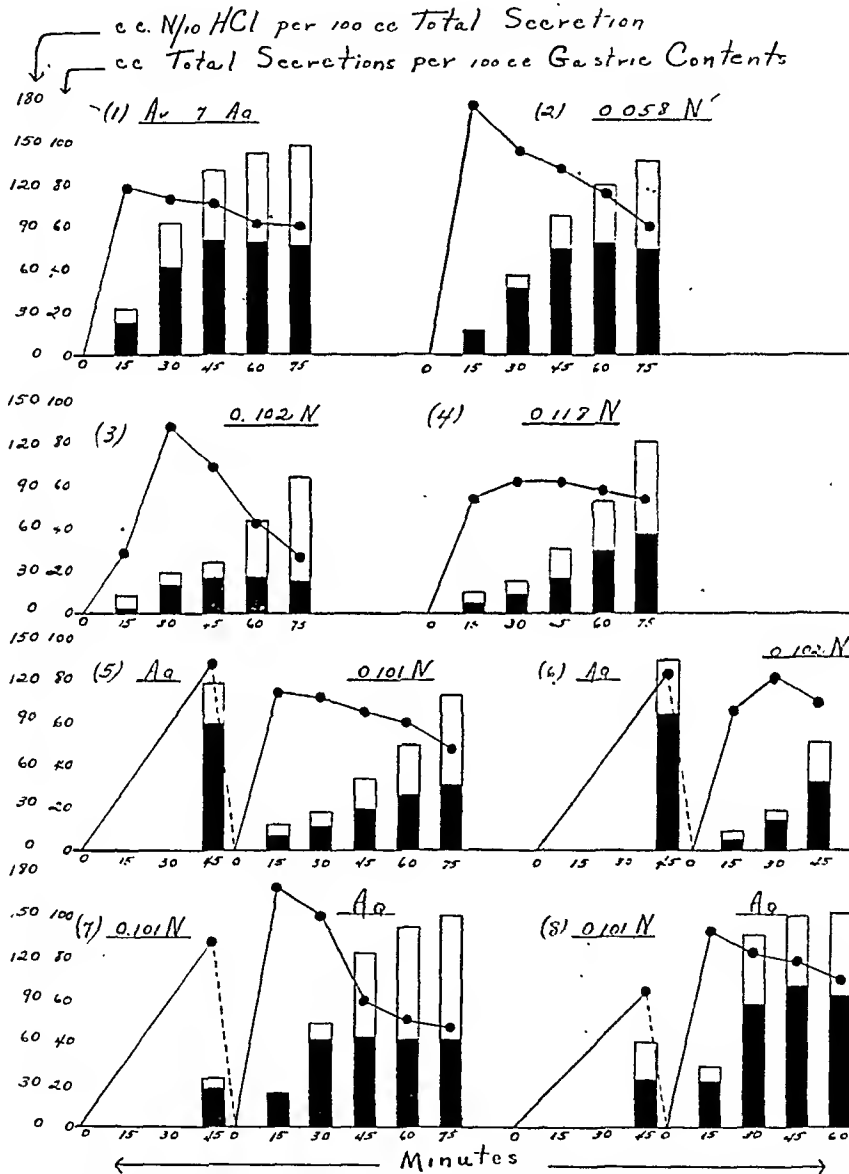


Fig. 1. Shows a series of experiments on the same subject. Full description is given in the text. The height of the columns shows the cc. of total secretions per 100 cc. of gastric contents. The black portion represents the cc. of acid secretion and the white portion the cc. of non-acid secretion. The dots and solid lines show the acidity of the total secretions expressed as cc. of N/10 HCl per 100 cc. These insignia are the same in Figs. 2 and 3.

more significant than Type I because acid inhibition must normally exert its effect at a time when acid is being secreted at a high rate. The details of procedure were as follows: The resting stomach was thoroughly lavaged with 300 cc. of the aqueous meal, the lavage was then removed and 800 cc. of aqueous meal introduced. The aqueous meal was allowed to remain in the stomach for from 30 to 45 minutes at which time it was removed as completely as possible and the stomach thoroughly lavaged with 300 cc. of the acid meal to be used. After thoroughly mixing, the lavage was completely removed and 800 cc. of the acid meal introduced. Samples (35 cc.) were removed every fifteen minutes.

(B) Results

Fig. 1 shows a series of experiments on the same individual. Graph 1 shows the average of 7 experiments in which the aqueous Liebig's extract test meal

was used. It is seen that the acidity of the gastric contents, expressed in terms of the pure acid secretion, reaches an average maximum of 53 cc. (equal to 90 cc. of N/10 HCl per 100 cc.), after which it remains almost constant until emptying occurs.

Graph 2 shows an experiment in which 800 cc. of a 0.058 normal acid test meal were used. It is seen that the amount of acid secretion per 100 cc. of gastric contents is practically the same as with the aqueous meal. In other words 0.058 normal acid is definitely below the threshold value and exerts no inhibiting influence on acid secretion in this individual.

Graph 3 shows an experiment in which an 0.102 normal acid meal was used. It is seen that the amount of acid secreted is definitely reduced, the maximal amount being less than one-third the average amount secreted with the aqueous meal.

Graph 4 shows an experiment with an 0.118 normal

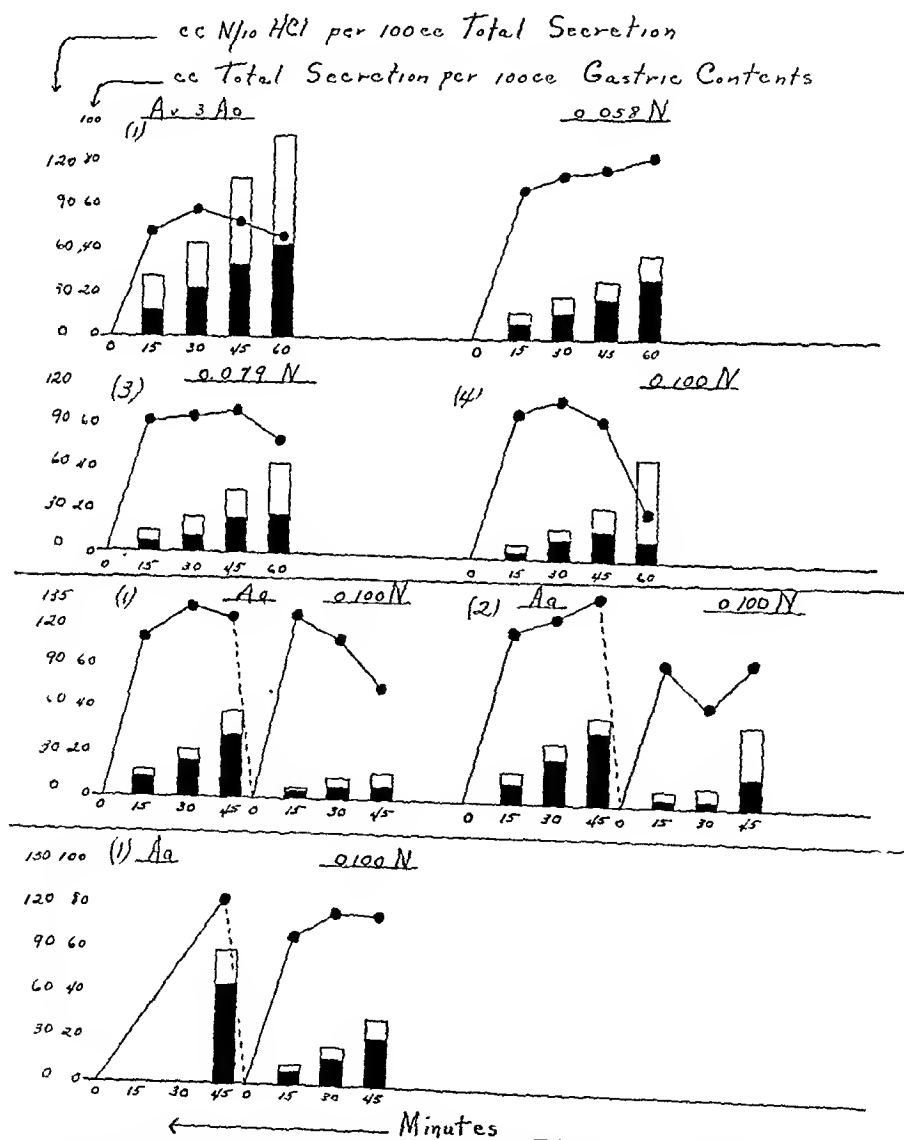


Fig. 2. Shows a series of experiments on three different subjects. Full description is given in the text. The insignia are the same as in Fig. 1.

acid meal. When compared with the aqueous meal it is evident that marked inhibition had occurred. When compared with the 0.102 normal acid meal, however, it is seen that definitely more acid was secreted when the acid meal of higher strength was used. This has often been observed and it indicates that the threshold for acid inhibition had shifted and was higher in experiment 4 than in experiment 3.

Graphs 5 and 6 show two experiments in which the aqueous meal was introduced first and allowed to remain for 45 minutes. After removal of the aqueous meal the acid meal was introduced. It is seen that marked and rapid inhibition of acid secretion occurred in spite of the fact that the rate of acid secretion had been very high with the aqueous meal.

Graphs 7 and 8 show two experiments in which the acid meal was introduced first and allowed to remain in the stomach for 45 minutes. After complete removal the aqueous meal was introduced. It is seen that the inhibitory effect terminated very promptly after removal of the acid meal, there being no hang over of the inhibitory action. This fact, plus the rapidity of the onset of acid inhibition, suggests that acid inhibition occurring in the stomach is a reflex rather than a hormonal mechanism.

Fig. 2, Graph 1 (upper third) shows the average of

three experiments in which 800 cc. of the aqueous meal were used.

Graph 2 (upper third) shows an experiment on the same subject in which 800 cc. of an 0.058 normal acid meal were used. It is seen that an acid meal of this strength produced a very definite decrease in the rate of acid secretion in this subject. (Compare with the subject shown in Fig. 1 (Graph 2) in whom this strength of acid caused no inhibition).

Graph 3 (upper third) shows an experiment on the same subject in which 800 cc. of 0.079 normal acid meal were given. A definite decrease in the rate of acid secretion is again observed which appears to be slightly more marked than with the 0.058 normal acid meal.

Graph 4 (upper third) shows an experiment on the same subject in which 800 cc. of an 0.10 normal acid meal were given. When this experiment is compared with the others performed on the same subject, it is seen that the decrease in the rate of acid secretion was very pronounced and definitely greater than it was with the 0.058 and 0.079 normal acid meals. In this subject there is evidence of a progressive decrease in the rate of acid secretion as the strength of the acid meal is increased.

Graphs 1 and 2 (middle third) show two experiments on another subject. In Graph 1, 800 cc. of the

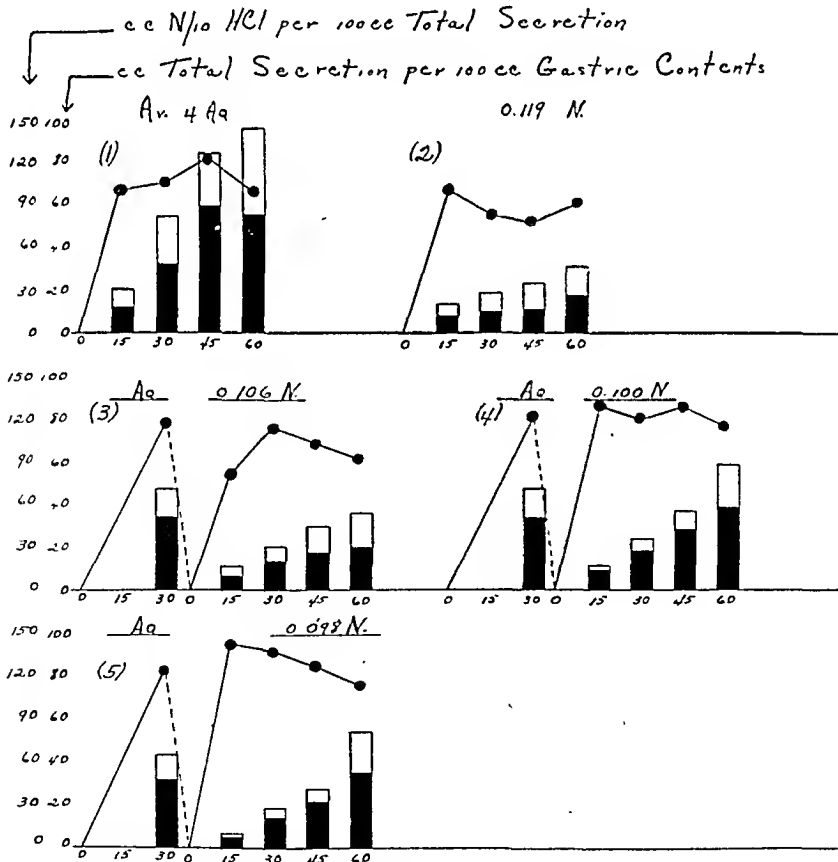


Fig. 3. Shows a series of experiments on the same subject. Full description is given in the text. The insignia are the same as in Fig. 1.

aqueous meal were first introduced and samples removed every 15 minutes for 45 minutes, at which time the aqueous meal was completely removed and 800 cc. of an 0.10 normal acid meal introduced. The decrease in the rate of acid secretion in this subject is seen to be more pronounced than in any others previously shown. In Graph 2 a somewhat different type of experiment was performed. 800 cc. of the aqueous meal were introduced and samples removed every 15 minutes for 45 minutes. The stomach was then emptied and 260 cc. of contents (meal plus secretions) were removed. The stomach was then lavaged with the acid meal and 260 cc. of acid meal introduced and samples removed every 15 minutes for 45 minutes. At the end of 45 minutes the stomach was emptied, the total volume of contents (meal plus secretion) removed

but the inhibitory effect is definitely less than in the subject shown in the middle third.

Fig. 3 shows a series of experiments on the same subject. Graph 1 shows the average of 4 experiments in which 800 cc. of the aqueous meal were used.

Graph 2 shows an experiment in which 800 cc. of an 0.119 normal acid meal were given. The decrease in the rate of acid secretion is seen to be very pronounced.

Graphs 3, 4 and 5 show experiments in which 800 cc. of the aqueous meal were introduced and allowed to remain for 30 minutes at which time the aqueous meal was removed and acid meals introduced. A definite decrease in the rate of acid secretion occurred in all experiments. The decrease was most pronounced with the 0.106 normal acid meal (Graph 3). In the

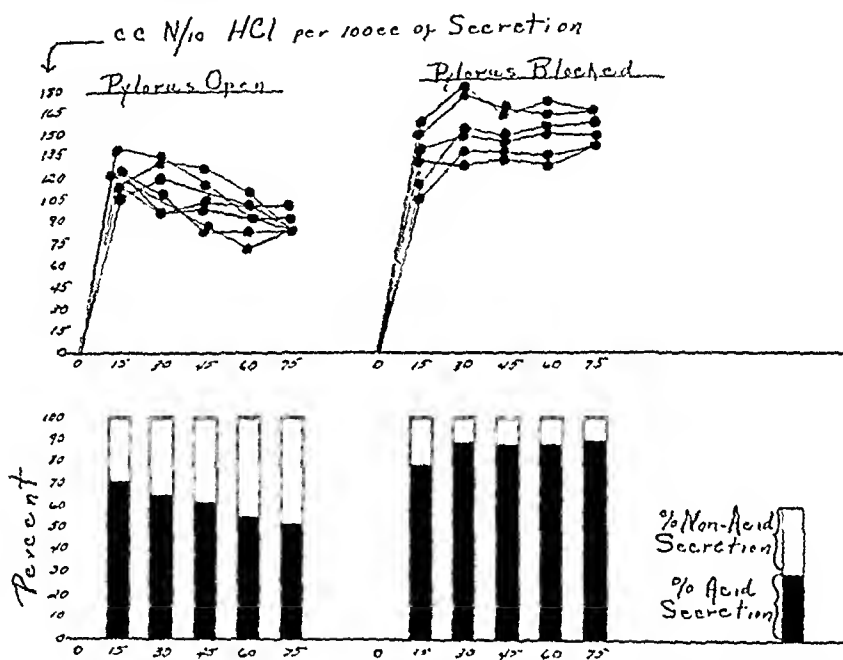


Fig. 4. Shows a series of experiments on a subject with a high rate of acid secretion with the pylorus open and with the pylorus blocked by means of a balloon. The upper half shows the acidity (cc. of N/10 HCl per 100 cc.) of the secretions entering the stomach. The lower half shows the average percentage composition of the secretions entering the stomach.

being 25 cc. In this experiment the volume of gastric contents was the same in the 45 minute aqueous sample and the 15 minute acid sample. Also the total volume of gastric contents in the 45 minute acid meal sample was about one-tenth the volume of the 45 minute aqueous meal sample. This experiment proves conclusively that the smaller amount of acid secretion, per 100 cc. of gastric content, observed with the acid meals is not due to the fact that the acid meals left the stomach more slowly and hence caused a lowering of the amount of acid secretion simply by dilution with a greater amount of test meal. This point will be discussed in greater detail later on.

Graph 1 (lower third) shows an experiment on another subject in which 800 cc. of the aqueous and acid meals were given. A marked decrease in the rate of acid secretion occurred when the acid meal was given,

experiments with the 0.10 normal and the 0.098 normal acid meals (Graphs 4 and 5) the decrease was much less marked so that at the end of 60 minutes (with the acid meals) the amount of acid secretion is about the same as at the end of 30 minutes with the aqueous meal. In general this subject had a rather high threshold for acid inhibition.

DISCUSSION OF ACID INHIBITION

In experiments on acid inhibition it is very important to be certain that the acid meal does not leave the stomach at a much slower rate than the aqueous meal because if this occurs the decrease in the amount of acid secretion, per 100 cc. of gastric contents, may be due to the fact that the acid secretion is diluted with a larger amount of test meal. In the experiments shown in Figs. 1, 2 and 3, the emptying time was the

same with the acid meal as with the aqueous meal; hence this factor was eliminated. In the experiment shown in Fig. 2 (Graph 2, middle third) this factor of greater dilution of the acid secretion was eliminated by a special type of experiment as described above. In dogs, acid test meals leave the stomach much slower than aqueous meals, the increase in the emptying time being directly proportioned to the strength of acid meal used. Because of this fact it was necessary, in previous work on dogs (1, 2) to use an entirely different type of statistical analysis to demonstrate the phenomenon of acid inhibition.

The effect of acid test meals on the amount of non-acid secretion entering the stomach is somewhat ir-

regular. For example, an 0.058 normal acid meal may cause definite inhibition in one subject (Fig. 2, Graph 2, upper third) and no inhibition in another (Fig. 1, Graph 2), while the degree of inhibition with an 0.10 normal acid meal shows great variations in different subjects. In general subjects who have high acid values with the aqueous meal show less acid inhibition than those who have low values. From this it follows that the threshold value for acid inhibition may be an important factor in determining whether a subject will have a high or low acid curve.

The rapidity with which acid inhibition occurs and the fact that an acid test meal shows no hang over of the inhibitory effect (Fig. 1, Graphs 7 and 8) suggest

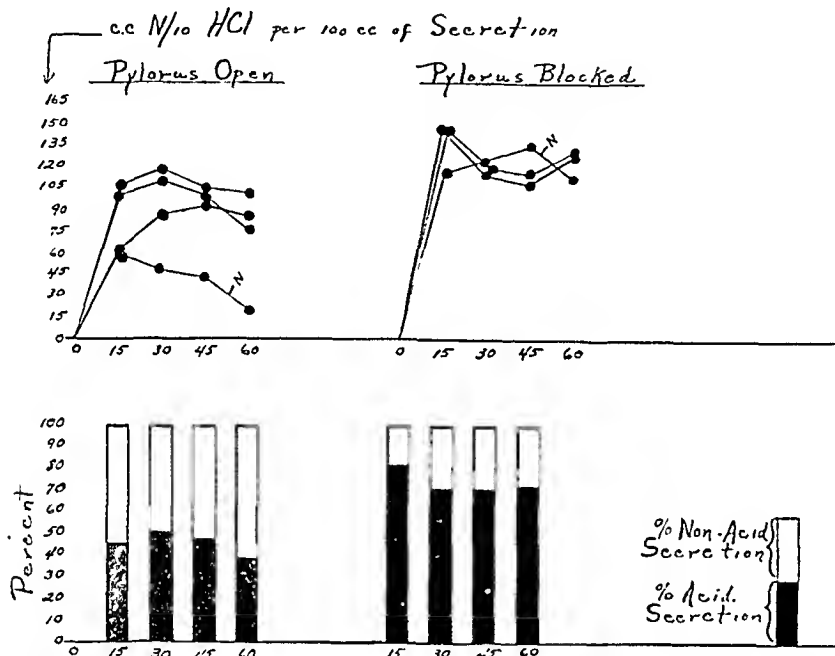


Fig. 5. Shows a series of experiments on a subject with a low rate of acid secretion with the pylorus open and with the pylorus blocked by means of a balloon. The upper half shows the acidity (cc. N/10 HCl per 100 cc.) of the secretions entering the stomach. The lower half shows the average percentage composition of the secretions entering the stomach. In the experiments marked (N) the subject was nauseated but did not vomit.

regular. It is either reduced almost as much as the acid secretion or else unchanged. It is practically never increased. In dogs it is usually unchanged (1).

The acidity of the total secretions entering the stomach shows irregular changes when acid inhibition occurs, the irregularity depending upon the changes in the amount of non-acid secretions in relation to the acid secretions. In experiments on dogs (1) it was possible to show quite definitely that when acid inhibition occurs, the concentration of the pure acid secretion is unchanged, the total amount of acid secreted is simply greatly reduced. The present experiments indicate that this is also true in the human subject.

The present experiments show quite clearly that the threshold for acid inhibition varies in different indi-

viduals, originating in the stomach (3), is brought about through nerve impulses and not by a hormone liberated into the blood stream.

In summary it may be stated that acid inhibition controls primarily the acidity of the gastric contents (cc. of acid secretion per 100 cc. of gastric contents) by regulating the amount of acid secreted.

DUODENAL REGURGITATION

(A) Methods

The stomach was blocked off from the duodenum by means of the balloon of a Miller-Abbott duodenal lumen tube (4). The balloon was placed practically at

3. Previous experiments on dogs (2) showed that the presence of acid in the upper intestine inhibits the intestinal phase of gastric secretion. The evidence suggested that this effect was possibly due to the liberation of a hormone from the upper intestine.

4. We used the type with the perforations distal to the balloon.

the pyloric sphincter so that the tip of the tube was in the beginning of the duodenum. The ordinary Levine tube was inserted through the nose into the stomach and the gastric samples collected in the usual manner. It was very difficult to perform satisfactory experiments because of the following facts: (1) It was often impossible to keep the balloon in the correct position since it tended to be regurgitated back into the cavity of the stomach or to move on down the duodenum. When the latter event occurred a blocked segment of duodenum was connected to the stomach and since the tube kept the pylorus open large amounts of duodenal secretions would regurgitate into the stomach. (2) Distention of the balloon sufficient to prevent passage of meal or duodenal secretions around it often caused nausea and vomiting which necessitated terminating the experiment. (3) It often happened that the pylorus relaxed progressively as the experiment progressed and allowed passage of meal and duodenal secretions around the balloon.

The details of the technique were as follows: After the balloon of the Miller-Abbott tube was in the correct position, the Levine tube was passed through the nose in the usual manner, 300 cc. of the test meal were then introduced and the stomach thoroughly washed. The lavage was then completely removed and the aqueous two per cent Liebig's extract test meal introduced. Since no emptying occurred during the experiment the amount of test meal used was reduced to 400 cc. Gastric samples were withdrawn every fifteen minutes. The same amount of gastric contents was removed every fifteen minutes and was of such a quantity that the stomach was emptied in the same time previously observed on the subject with the pylorus open. During the test, duodenal contents were frequently withdrawn through the Miller-Abbott tube and tested for phenol red to see whether any test meal was passing the balloon. The gastric samples were tested for bile by the Pettenkofer test. It was often found that small amounts of meal passed into the duodenum and small amounts of duodenal secretions entered the stomach but when this occurred to only a slight degree the experiment was considered satisfactory.

(B) Results

Two subjects were selected for intensive study. One subject had a high rate of acid secretion and the other a comparatively low rate.

The acidity of the gastric contents (meal plus secretions), in these experiments with the pylorus closed, cannot be compared with the acidity of the gastric contents in experiments on the same subject with the pylorus open because widely different amounts of test meal are present in the stomach to dilute the acid secretion. This is due not only to the fact that emptying did not occur in experiments with the pylorus blocked but also to the fact that different amounts of meal were introduced into the stomach. However, the acidity and composition of the total secretions entering the stomach are independent of the amount of test meal in the stomach and are strictly comparable in the two sets of experiments.

Fig. 4 shows 7 experiments with the pylorus open and 6 experiments with the pylorus blocked on the subject with the high rate of acid secretion. In the

upper part of the figure the acidity of the total secretions entering the stomach is shown under the two conditions. With the pylorus open the acidity of the total secretions reaches its peak in the first or second fifteen minute period after which there is a progressive decrease until the stomach empties. With the pylorus blocked the acidity of the total secretions rises rapidly to a high value and remains at this level until the stomach is emptied. In the lower part of the figure the per cent of acid and non-acid secretion in the total secretion entering the stomach is shown. With the pylorus open there is a progressive increase in the per cent of non-acid secretion until in the last samples the non-acid secretions average 46 per cent of the total secretions. With the pylorus blocked the per cent of non-acid secretion remained practically constant, after the first fifteen minute period, and averaged about 10 per cent of the total secretion entering the stomach.

The subject with the low rate of acid secretion (Fig. 5) showed virtually the same findings. However, due to the lower rate of acid secretion the non-acid secretions of intragastric origin were of relatively more importance; hence it is seen that the acidity of the total secretions does not rise as high, when the pylorus is blocked, as it did in the subject with the high rate of acid secretion. The two experiments marked (N) are very instructive. In these the subject was nauseated during the entire period but did not vomit. When the pylorus was open the nausea resulted in the regurgitation of large amounts of non-acid duodenal secretions which rapidly lowered the acidity of the total secretions. When the pylorus was blocked, however, the nausea resulted in practically no increase in the non-acid secretions of intragastric origin; hence the acidity of the total secretions remained high. In this subject, with the pylorus open, the non-acid secretions averaged 61 per cent of the total secretions in the last samples obtained, while with the pylorus blocked the non-acid secretions averaged only 28 per cent of the total secretion at the same period.

DISCUSSION OF DUODENAL REGURGITATION

The above experiments show very definitely that in the two subjects studied duodenal secretions normally regurgitated into the stomach and lowered the acidity of the total secretions by dilution and neutralization. When duodenal regurgitation was prevented the non-acid secretions of intragastric origin were too small in amount to cause a definite decrease in the acidity of the total secretions. When the rate of acid secretion is low, the non-acid secretions of intragastric origin are of relatively more importance than when the rate of acid secretion is high.

It is quite probable that the amount of duodenal secretions regurgitated and the amount of non-acid secretions of intragastric origin may both vary in different subjects; hence, broad generalizations are not justified on the basis of experiments on two subjects. However, the present experiments show very clearly that duodenal regurgitation is a normal event and that its chief effect is to lower the acidity of the total secretions entering the stomach.

In previously reported experiments (4) dogs were studied before and after the Mann-Williamson operation in which the duodenal secretions are drained into the terminal ileum. These experiments gave results

which were practically identical with the present ones on human subjects.

GENERAL DISCUSSION

Acid inhibition controls primarily the acidity of the gastric contents (cc. of acid secretion per 100 cc. of gastric contents). In previous studies (4) it has been shown that acid inhibition can control the acidity of the *gastric contents* when duodenal regurgitation is entirely prevented.

Duodenal regurgitation controls primarily the acidity of the total secretions entering the stomach and may or may not influence the acidity of the gastric contents.

It is quite likely that the relative importance of these two mechanisms may vary in different normal subjects. In disease it is theoretically possible to have failure of one mechanism but not of the other. If duodenal regurgitation did not occur but if acid inhibition was normal, then the secretory curve would show a high and maintained value for the acidity of the *total secretions* entering the stomach, but a normal value for the acidity of the *gastric contents*. On the

other hand, if duodenal regurgitation was normal, but if acid inhibition failed to function, then the secretory curve would show a normal behavior of the acidity of the *total secretions* entering the stomach but a high value for the acidity of the *gastric contents*. These anomalies of the gastric secretory curve have been produced under experimental conditions in dogs (7).

SUMMARY

Acid inhibition and duodenal regurgitation have been shown to play important roles in the regulation of the gastric secretory curve in the normal human subject.

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Treatment

A Note on the Use of Nitroglycerin in the Immediate Treatment of Acute Non-Hemorrhagic Pancreatitis*

By

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THERE is an increasing tendency to treat acute pancreatitis at least during the acute attack by non-operative means, particularly when the seizure is known to be of the transient type, which has been designated by various terms such as acute interstitial, edematous, or non-hemorrhagic pancreatitis (1). Although there is ample evidence that the attack ultimately subsides often within a few hours or days there has been no specific therapy designed to relieve the lesion causing the severe symptoms. This is due to the fact that the pathogenesis is still unestablished. One of the theories, however, assumes that there is a reflux of bile into the pancreas due to spasm of the sphincter of Oddi, thus provoking an acute inflammation of the pancreas; the evidence in favor of this idea has been discussed elsewhere (2). If this theory is correct, relaxation of the sphincter of Oddi should prove effective in relieving symptoms. Recent observations on the human biliary tract have shown that at least two pharmacological agents are of influence, i.e., morphine increases whereas the nitrites decrease spasm of this muscle. (Best and Hicken (3), Doubilet and Colp (4), McGowan, Butsch and Walters (5)). These findings explain the frequent failure of morphine to relieve pain in these patients; they likewise point to the nitrites as an effective therapeutic agent in its treatment. In a recent known case of acute interstitial pancreatitis the use of nitroglycerin was so

effective in relieving the attack that it seemed important to describe the observation.

The patient, a 21 year old, unmarried, female, had had severe attacks of epigastric pain associated with nausea and vomiting for many years. An appendectomy was performed without influencing the frequency of the attacks which varied in intensity but were often absent for months at a time. During one very severe attack she was admitted to Barnes Hospital where she showed a tremendously (5 + normal) high value of blood amylase, which, however, returned to normal with subsidence of the seizure which lasted 36 hours and was uninfluenced appreciably by any sedatives. During her stay a definite Head zone of hyperesthesia was made out over her left hypochondrium. She was discharged and remained well except for occasional attacks lasting only a few hours. Cholecystogram showed a normal shadow.

On February 10, 1938, she had another very severe attack in all respects the same as the one for which she was hospitalized 2 years previously. I saw her at home and examination was identical with the findings during her former seizure. She was immediately allowed to inhale the contents of one ampoule of amyl nitrite and at five minute intervals 1/200 grain tablets of nitroglycerin were allowed to dissolve under her tongue. By the time the third tablet was given the pain was practically gone and within a half hour the patient was entirely comfortable and later fell asleep and slept all night.

The response to this medication was so dramatic that it would seem to be indicated in selected patients suspected of having this disease, which, as has been pointed out (1) often masquerades as biliary colic.

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perforated peptic ulcer or intestinal obstruction. In this connection it is of interest to note that glyceryl nitrate (nitroglycerin) has been used therapeutically in biliary colic by Best and Hicken (3) who observed emptying of the common duct (visualized by opaque oil) within 10 minutes after placing 1/100 grain of this drug under the patient's tongue.

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We recently saw a patient with migraine whose attacks appeared to be stopped for three months while she was taking emmenin. They didn't come back until three months had lapsed after she stopped taking the medicine. Whether this effect can be secured often or not we cannot tell.

Many physicians are much afraid of barbiturates, fearing that they will produce habituation. It is doubtful if a barbiturate ever produces typical withdrawal symptoms. In our experience the only thing that happens on withdrawal is that the patient cannot sleep, but this is not surprising. Usually all one has to do is to switch to chloral or paraldehyde, and all is well. In 1937, Swanson, Weaver and Chen made extensive studies on dogs which indicated there is no habituation after the prolonged use of sodium amytal. This agreed with the results of similar studies made by others.

NEW TREATMENT FOR WORMS

Recently a man and wife came from South America complaining of nervous troubles. The man's stools contained ova of *Ascaris lumbricoides* together with some amebae. The wife's stools showed only the amebae and some *Trichiuris*. The man had to be given two courses of hexylresorcinol before a few worms could be obtained, and he found the treatment pretty hard on his digestive tract. The wife was given six tablets of treparasol and without purgation or discomfort she promptly passed several *Ascaris*. The conclusion of the two patients was that treparasol was by far the more satisfactory treatment for the worms.

Another patient was seen with a tapeworm, the head of which had hung on in spite of many efforts on the part of physicians to dislodge it. The man then happened to come in off the desert one day tremendously thirsty so that he downed about a gallon of root beer, whereupon the worm promptly gave up and came away entire!

On rare occasions, one will see a patient with a tachycardia which is practically constant with a rate around 120. We have seen two such cases in which out of many drugs tried the only one that had any effect was gynergen. In small doses this brought the pulse rate down to about 90 a minute and gave the patient great comfort. It is questionable, of course, how long the use of the drug could be kept up. The fact that gynergen helped in these cases suggests that the cause was an overly active cardiac accelerator nerve.

UNCOMFORTABLE REACTIONS WITH NICOTINIC ACID

Not every physician has been warned that in some persons the first dose of nicotinic acid will produce a reaction which is so unpleasant and so startling that the patient will think he is going to die, and the doctor may be inclined to agree with him. It would doubtless be well to warn sensitive patients that within a few minutes after swallowing the first pill of 50 mg. they may feel an intense burning all through the body. In a patient just seen the reaction faded out in about three hours without any medication. It might be well to begin always with a small dose to see if the patient has an idiosyncrasy to the drug.

Nicotinic acid should be tried in all puzzling cases of diarrhea because occasionally it will promptly bind the bowel so that the patient will return in a few days asking for a laxative.

In the Proceedings of the Royal Society of Medicine for August, 1938, Glover summarized a study of tonsillectomy in England and Wales. His conclusion is that it is a little difficult to believe that among the mass of tonsillectomies performed today all subjects for operation are selected with much discrimination. He could not avoid the conclusion "that there is a tendency for the operation to be performed as a routine prophylactic ritual for no particular reason and with no particular result."

Editorials

A POWERFUL DEPRESSANT OF GASTRIC SECRETION

TO the gastro-enterologist, one of the most hopeful and thought-stimulating papers published in recent years is that of Gray, Wiczorowski and Ivy in *Science* for May 26, 1939. As most clinicians know, Dr. Ivy and his associates have for some time been purifying and studying the substance now called enterogastrone which can be extracted from the mucosa of the upper end of the small bowel. It was shown in 1926 by Farrell and Ivy that the secretion in and the motility of a transplanted and denervated gastric pouch can be

inhibited by the ingestion of fat. Evidently there is some substance in fat which can go through the blood and can exert a hormonal type of effect. Later in Lim's laboratory in China it was found that this effect could be produced by a substance which can be extracted from the mucous membrane of the duodenum.

Recently Ivy and his associates have found that this substance, now called enterogastrone, consists of two substances, one which inhibits secretion and the other which inhibits motility.

Following the suggestion obtained from the work of Sandweiss, Saltstein and Farbman, who found that

extracts of pregnancy urine will prevent the development of jejunal ulcers in dogs previously subjected to the Mann-Williamson operation, Culmer, Atkinson and Ivy administered such extracts to dogs with a Pavlov pouch and found an immediate and significant reduction in gastric secretion. Necheles reported extraction from human urine of a substance which inhibits gastric secretion, and Sandveiss and his associates also found that extracts from the urine of normal women is potent in preventing experimental ulcers in dogs.

Now, Gray, Wiczerowski and Ivy find that extracts of normal male urine are highly potent in inhibiting gastric secretion. Three milligrams of solid material obtained from 150 cc. of urine contain one "enterogastrone unit" which, when injected into a dog, will reduce gastric secretion by one-half. This material is approximately sixteen times as potent as the material which had previously been prepared from the duodenal mucosa, and fortunately it is much freer from undesired constituents. Fortunately also, it has been found that dogs which had become refractory to injections of enterogastrone prepared from the mucosa would still respond to extracts prepared from urine. It is fortunate also that the substance that is prepared from urine does not affect the motility of the stomach, and it is very fortunate that it is not injured by boiling for five minutes. As yet it is not known if this substance is the essential principle of the one that is obtained from the duodenal mucosa.

Walter C. Alvarez, Rochester, Minn.

THE EFFECTS OF SPLANCHNICOTOMY ON THE DIGESTIVE TRACT OF MAN

IN the *Annals of Internal Medicine* for June, 1938, Allen and Adson reported on 311 operations performed on 156 patients for the relief of hypertension. In these operations the splanchnic nerves on both sides were cut. In a number of instances there was a temporary loosening of the bowels with three or four soft movements a day. In many instances constipation was relieved. Flatulence or other signs of disturbed activity of the digestive tract were uniformly absent. It seems obvious, then, that in man, much as in cats and dogs, the main sympathetic nerves of the abdomen can

be dispensed with without any resultant disturbance in health.

In the rabbit double splanchnicotomies is a serious operation with a high mortality. The animals usually suffer with diarrhea and they lose tremendously in weight, probably because the highly important cecum is immediately emptied. Studies on such animals indicated that a normal brake-like action of the sympathetic nerves had been removed. The bowel was extremely irritable, and the slightest touch could throw it into a spasmodic contraction.

Walter C. Alvarez, Rochester, Minn.

THE DANGER AND FOLLY OF GIVING A BARIUM MEAL TO PATIENTS WITH INTESTINAL OBSTRUCTION

WE have recently been impressed several times with the need for gastro-enterologists' warning their assistants never to give a barium meal in the presence of symptoms and signs suggesting intestinal obstruction. Time and again we have seen such lack of thoughtfulness on the part of some interne or assistant seal the fate of a poor patient. Perhaps the barium coming down into an almost obstructed segment caused complete blockage with symptoms so acute that the surgeons could not operate, or more often perhaps, in cases of carcinoma of the colon, we have seen the patient lose his life because the surgeon had to open the bowel widely and spend much time digging out large fecaliths cemented together with barium.

The saddest feature of many of these cases was that the carcinomatous obstruction could so easily have been felt and located if the interne had explored the rectum with his finger or looked in with the sigmoidoscope. In other cases the obstruction could easily have been located with the help of a "dial film," or a film taken after giving the patient a teaspoonful of barium, or just enough to outline the walls of the bowel.

Finally, no roentgenologist should ever fill with barium the colon of a child with Hirschsprung's disease without personally seeing to it afterward that the material was removed. Disaster has followed in some cases in which this precaution was not taken.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

Bile, Its Toxicity and Relation to Disease. By O. H. Horrall, Chicago, University of Chicago Press, 434 pp., 1938. Price \$4.00.

THIS is a splendid monograph based upon a review of over 2,000 books and articles. As Horrall points out in the opening chapter, it is a remarkable fact that from the dawn of history until the coming of scientific medicine in the 18th century, a large percentage of the diseases of man were supposed to be due to the presence in the body of toxic bile, either yellow or "black." In fact, today, in our common speech we still say that a man is bilious or he is in a melancholy mood or he is choleric or we say that cholera is raging in India. The Mexican patient in Los Angeles when asked by his physician what the trouble is will commonly answer that he has had a rush of bile to his brain.

In this book Horrall summarizes everything that is really known about the toxicity of bile and how this substance can injure the body. There is no question that bile or its salts when present in excess in the blood can produce injuries in many parts of the body and can produce peculiar symptoms. Curiously, of late it has been found also that the presence of bile or of an injury to the liver producing jaundice will sometimes bring great relief from pain. It can bring remarkable relief of distress to the arthritic patient, and it can relieve migraine. We can remember years ago seeing a boy who had been cured of a severe epilepsy by the establishment of a biliary fistula. When this fistula was closed the fits returned and the family then asked that the common duct be drained again. Perhaps it was an observation of this sort that

caused Hippocrites to believe that mental depression was due to the presence of black bile in the blood vessels of the brain.

This is a book to be placed on the shelf of everyone who does research in the fields of digestive tract physiology, pathology and surgery.

Erkrankungen Der Verdauungsorgane—Third volume of the Handbuch der inneren Medizin. By Julius Springer. Edited by G. v. Bergmann and R. Stachelin. Published in two parts. Berlin, 1514 pp., 1938. Price 117 RM (bound).

One of the finest books ever written on the diseases of the digestive tract is this huge third volume of Bergmann and Stachelin's "Handbuch der inneren Medizin." It is now in the third edition. The two big books that make up the "volume" are beautifully printed and beautifully illustrated. The reproductions of roentgenograms are excellent, and there are some beautiful colored plates.

In the first volume one finds articles on teeth, the mucous membrane of the mouth, the tongue, the salivary glands, the esophagus, and the stomach. Again Dr. Katsch has taken most of the responsibility for the articles on the stomach. Doctors Kalk and von Bergmann have helped. In the second volume one finds articles by Henning and Baumann on diseases of the bowel and the diaphragm. Drs. Katsch and Brinck have written on diseases of the pancreas, and Dr. Stroebe and Dr. Schwiégk have written on the liver and the biliary passages.

If a gastro-enterologist were to have to limit himself to one book, and if he could read German, this might well be the volume of his choice not only because of the enormous amount of information supplied but because of the extensive bibliographies at the ends of the chapters. On reading here and there one is pleased to find many signs of up-to-dateness in the articles. All in all these two volumes cannot be praised too highly. They are truly encyclopedic in quality.

The Surgery of Pain. By René Leriche. Translated and Edited by Archibald Young. Baltimore, Williams & Wilkins Company, 512 pp., 1939. Price \$6.50.

One can perhaps get some idea of the value of this large book by noting that a surgeon as eminent and as busy as Archibald Young of Glasgow thought it worth while to spend his valuable spare time in translating it. As everyone knows, Leriche was one of the pioneers in the surgery of the sympathetic nervous system. Between 1910 and the time of writing this book he performed 46 symplectomies or cord sections, 53 peripheral neuroto-

mies, 201 retro-Gasserian neurotomies or excisions of the Gasserian ganglion, and over 500 operations on sympathetic nerves.

As he says, neurologists have long neglected the study of the autonomic nervous system because the syndromes produced by disease in this system were not obviously nervous in nature. Leriche believes that a more thorough understanding of the sympathetic nervous system will throw light on such puzzles as the bilateral effects of many sympathectomies, the progressive spread of certain pains, their passage to the side opposite to that where they originated, the disturbing mental effect produced quite

early by certain pains, and the apparently thalamic localization, at an early stage, of certain post-traumatic pains.

One good thing about this book is that Leriche has based it largely on his own experience, and he is not ashamed of using the personal pronoun. He believes that the impersonal book is often dull and boring. "The book which is destined to become a classic . . . can only be a personal work in which the open mind of the author asserts itself, with the obvious desire of driving home an individual point of view. Such a book must bear the personal imprint of the writer."

Although the book runs to 512

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¹ Mutch, N.: *Brit. M. J.* 1:143, 205, 254, 1936.

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MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

pages, Leriche admits that he had to leave out a number of subjects. He did not discuss the pains of tabetics because he no longer believes that they should be treated surgically. He didn't discuss the pains of thalamic origin, or the pains of angina pectoris and herpes zoster because he didn't know enough about them.

Every neurosurgeon and every student of abdominal pain will want to read at least some of the chapters in this book.

First and Second Interlinear German Readers. By Meno Spann, Chapel Hill, University of North Carolina Press, 1938.

One of the greatest handicaps of the physician who wants to do some research and wants to keep up with what is going on medically in Europe is the lack of a good reading knowledge of German. Almost every physician today has had a few years of German in high school or college, but unfortunately most of the class-room

time was taken up with the study of dry grammar, and as a result, the ability to read the language, which was really the only acquirement needed and desired by the student, was not attained.

We have always wondered why teachers of languages have been so stupid and bullheaded that they wouldn't train students to read in the natural way of just having them read. If a boy of average intelligence were to read a language for four years he would almost certainly be able to go on reading. As it is today, he graduates with too small a vocabulary for reading, too little of the feel of the language, and almost complete oblivion of the grammatical rules which he struggled over for four years.

Not only do teachers of language object to the students learning to read but they insist on putting a large obstacle in his way. They insist with vehemence that he spend most of his time looking in the dictionary for meanings of words when all this time could be saved by supplying texts with the meanings of the words printed interlinearly. The grammar could then be mentioned in footnotes and picked up along the way just as a child picks it up when he learns a language.

With these ideas in mind we were delighted to find recently two little German readers by Meno Spann with an interlinear translation. A few readings of these readers would help physicians greatly in their work. Incidentally, a good text of this type is the German-English Vade-mecum by B. Lewis. Unfortunately it is now out of print and can be obtained only from second-hand dealers. It has excellent medical lectures in German on one side of the page and the English translation on the other.

Gastro-Intestinal Dysfunction. By Barton A. Rhinehart, Little Rock Arkansas, Central Printing Company, 311 pp., 1939.

This is a rather curious book in which the author tries to show that most gastro-intestinal troubles are functional in nature and most of them can be included in the one category of a deficiency state.

The first part of the book is filled with references from the literature which unfortunately are not always well quoted and are not strung together as well as they would be on a well defined thread which would serve to carry the reader easily along with a clear idea of where he is going. Actually, the reviewer had to turn to the back of the book and read a lot of case reports before he could understand what Dr. Rhinehart was trying to prove with his lot of quotations. Then he gained the impression that Dr. Rhinehart had tried to find facts

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with which to bolster his theory that all that most patients with indigestion need is to take calcium and irradiated ergosterol.

Usually after looking through a book of this type one ends up with the hope that the author is right, but with the feeling that he hasn't yet brought forward enough proof or presented this proof logically enough to satisfy most readers. The fact that many patients have seemed to get well under the treatment does not prove anything. If one is to depend on such proof then one must believe that Christian Science, osteopathy and chiropractic are good and useful forms of medicine. We fear that Dr. Rhinehart will meet with some doubting Thomases along the way.

Crystalline Enzymes. By John H. Northrop, New York, Columbia University Press, 176 pp., 1939. Price \$3.00.

This is a valuable and epoch-making monograph in that it sums up the results of years of brilliant research into the nature of the most important proteolytic enzymes of the body, pepsin, pepsinogen, chymotrypsinogen, chymotrypsin, trypsinogen, trypsin and carboxypeptidase. Northrop and his coworkers succeeded in crystallizing these substances and in learning a great deal about their chemical structure and the ways in which they work. The story is as interesting as many tales of adventure and geographic discovery. Dr. Northrop describes also some of his experiments which have thrown great light on the chemical nature of bacteriophage.

The books cling to the old statement that there is one proteinase trypsin, in the pancreatic secretion, but it is now known that there are several.

Every gastro-enterologist who wants to learn all he can of the workings of the digestive tract will want to own and read this book.

Abstracts

IVANCEVIC, I. UND KADRKA, S.

Vorgänge an der Magenschleimhaut unter dem Einfluss von Bittermitteln. Arch. Exp. Path. u. Pharmacol., 189(5/6):557-567, 3 figs., 1938.

By roentgenological relief methods characteristic changes of secretion on the inner surface of the human orthotonic stomach were shown following adm. of gentian extract. There was swelling of the mucosa and increased mucus secretion. The swelling was apparently due to direct action of the gentian; no indirect cause was determinable. The resulting increase of mucus secretion always followed direct contact of the bitter principle

with the mucosa. An indirect, central reflex mechanism, originating from the mucosa of the mouth, was not the rule, nor was it predominant. There was no evidence for reflex effect from the jejunum to alter the turgor of the mucosa or the secretion of mucus. The effect depended on manner of adm. and the dose. Within a certain range it was little dependent on the degree of turgor or development of mass of the mucosa. However, after attaining a certain amount of turgor there seemed to be a limit of reactivity to the gentian, because of the abnormally swelled state of the mucosa. The degree of swelling caused by gentian was greater than

that due to feeding eggs (digestion hyperemia). The difference was still more evident in the amount of mucus secreted. The swelling and mucus output quickly followed gentian adm. (3-8 min.). The maximum effect was in about 20-35 min.; followed by slow shrinkage of the mucosa and pyloric emptying of the mucus deposit; after 2 hrs. the initial state was reached. This course was broken if ingestion of eggs followed and the gradual increase of swelling and mucus output of the digestion process then took place. The direct swelling action of gentian and the increased mucus secretion were essentially similar in nature to normal digestion hyper-



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emia. The findings differed from previous reports as to the action of Amara. In the mechanism of action of bitters the direct local action on the gastric mucosa is of greater importance than is generally recognized.—C. S. L. (Courtesy Biol. Abst.).

DOUBILET, H. AND A. C.

The Response of the Smooth Muscle of the Gall Bladder at Various Intravesical Pressures to Cholecystokinin. Am. J. Physiol., 124(2):379-390, 5 figs., 1938.

The tension developed by the gall bladder when it contracts in response to a single submaximal dose of

cholecystokinin depends on the initial pressure. The optimal intra gall bladder pressure for an optimal contraction in response to a submaximal dose of the hormone was found to vary from 4 to 5.5 cm. of pressure (Sollmann-Rademacker's soln.) in the isolated vesicle of the guinea pig and from 5 to 15 cm. of bile pressure in the dog's vesicle in situ. When the pressure is optimal the vesical contracts more quickly than otherwise. The guinea pig's gall bladder failed to contract in response to the standard dose of the hormone when intravesical pressure was 12.5 cm.; this value for the dog was 25 cm. At

these high pressures a slight contraction was sometimes obtained when the standard submaximal dose of the hormone was increased from 2 to 4 times. If the gall bladder is "overstretched" by the relatively high pressure, then the viscus contracts less in response to the hormone. The range of optimal pressure for an optimal contraction is approximately the same as the optimal pressure for a tonus rhythm of optimal amplitude. This was found to be true of the isolated gall bladder of the guinea pig. If the gall bladder of the dog is subjected to a pressure of 30 or 40 cm. of bile for 2 hrs., it contracts less to the same dose of cholecystokinin than it did before. These observations must be considered in the interpretation of the response of the gall bladder to a agent.—Auth. (Courtesy Biol. Abst.).



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STAFFORD, EDWARD S.

Regional Ileitis and Ulcerative Colitis. Bull. Johns Hopkins Hosp., 62(4):399-407, 5 figs., 1938.

Ten cases of regional ileitis and 3 cases of ulcerative colitis in association with lymphogranuloma were discussed. The similarity of the clinical features were noted. The typical microscopical lesion of lymphogranuloma, described in one case, is differentiated from non-specific lesions of regional ileitis by the presence of tubercle-like groups of epithelioid cells with a central core of polymorphonuclear leucocytes. The virus of lymphogranuloma may cause the ulcerative lesions in the colon and the lesions of regional ileitis may be due also to a virus.—Auth. (Courtesy Biol. Abst.).

YOUNG, W. B., MEEK, W. J. AND HERRIN, R. C.

Extrinsic and Intrinsic Pathways Concerned with Intestinal Inhibition During Intestinal Distension. Am. J. Physiol., 124(2):470-477, 1938.

Motility of the jejunum above and below a distension was recorded by the use of 2 balloon-Hg-manometer systems in expts. on unmedicated dogs having 1 or 2 Thiry or Thiry-Vella fistulae. Denervations were done to permit separate evaluation of the role of intrinsic and extrinsic pathways in the responses observed. Distension of the jejunum of the dog results in inhibition of all types of movement and decreased tonus of the undistended part of the jejunum in both directions from the site of distension. The degree of inhibition depends upon the rapidity with which the pressure is increased in the balloon and upon the final pressure attained. The inhibition of the normal jejunum as a result of distension is accomplished primarily by means of

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reflexes over the extrinsic nerves. The jejunum contains afferent endings which are stimulated during distension and efferent nerve endings which have an adrenaline-like effect on the motor functions of the jejunum. When the extrinsic nerves are cut an intrinsic and less efficient mechanism for mediating intestinal inhibition during intestinal distension is unmasked. This pathway is presumably over the intrinsic nerve cells of the intestinal wall. When the extrinsic nerves are intact inhibition of the intestine during distension is accomplished as well in the absence of the intrinsic connections as when they are present.—W. B. Y. (Courtesy Biol. Abst.).

*HEILBRUN, NORMAN AND HUBBARD, ROGER.

An Experimental Study of the Biphase Van den Bergh Reaction. Am. J. Clin. Path., 8(8): 273-280, 1938.

When the bilirubin in the blood stream of normal patients or of patients with hemolytic jaundice is increased by injecting alkaline solns. of bilirubin, the time in which a color appears after the addition of the diazo reagent to plasma is decreased. The general type of reaction, however, does not resemble that seen in liver dystrophy and obstructive jaundice, for the color attains maximum values slowly. When the pig-

ment is present in high conc. the results satisfy the definitions of a biphasic reaction. Another type of biphasic reaction can be produced by injecting bilirubin into a patient with liver dystrophy or obstructive jaundice with low bilirubin concs. In such patients the pathological pigment reacts rapidly and the injected pigment reacts slowly. It is sometimes, but not always, possible to recognize this biphasic reaction just described because the unaltered injected or the delayed reacting pigment present may give a yellow color which obscures the characteristic pink of the immediate Van den Bergh reaction by a yellow or orange color.

Auth. summ.

*JOSEPHSON, B. AND LARSSON, H.

Elimination of Cholic Acids. Acta Med. Scand., 99(2/3):140-146, 1 fig., 1939.

Na cholate injected intraven. into man disappears very rapidly from the blood and is rapidly and quantitatively excreted by the liver in the bile. 5 minutes after injection the blood conc. is only slightly increased, and after 30 minutes the conc. value is normal again. After one hour most of the injected cholate can be recovered in the bile, partly in unconjugated form.

J. F. Wilkinson.

*LINDEBOOM, G. A.

Die Hippursäuresynthese als Leberfunktionsprobe. Acta Med. Scand., 99(2/3):147-161, 1939.

The excretion of hippuric acid after oral adm. of Na benzoate was found to be 3.7g (mean value) for normal controls. The test gave a positive result not only in many cases of primary liver disease (cirrhosis, hepatitis) but also in mechanical icterus, cardiac decompensation with congested liver and kidney disease. The value for the clinic was limited.

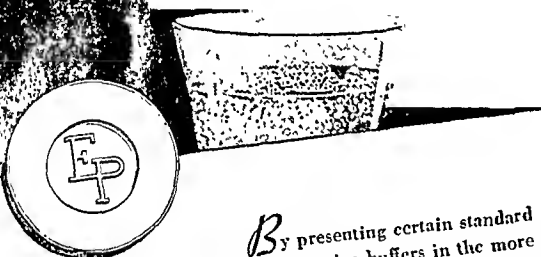
J. F. Wilkinson.

*LIUM, ROLF.

Etiology of Ulcerative Colitis. II. Effect of Induced Muscular Spasm on Colonic Explants in Dogs, with Comment on Relation of Muscular Spasm to Ulcerative Colitis. Arch. Internal Med., 68(2):210-225, 3 fig., 1939.

Colonic explants in dogs react to various stimuli by a spastic contraction of the musculature. Whether the spasm was evoked by mechanical stimulation, parasympatheticomimetic drugs or dysentery toxin, the result was damage to the overlying epithelium, with hemorrhage and ulceration. The mode of action of dysentery toxin in causing mucosal

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ulceration was apparently related to its injurious effects of muscular spasm. With muscular contraction of the explant secretion of mucus was immediately increased but with continued hyperactivity the secretion became thin, watery and inadequate for protective purposes. Ulcers were not covered with protective mucus until they healed. In the intact colon ulcers were constantly exposed to trauma from the passing fecal current. Even when the regenerated epithelium returned to a normal gross appearance it was more sensitive to trauma than the normal epithelium of the graft. Ulcerative colitis was thought to be a specific reaction to a number of in-

fluences which could initiate spasm of the colonic musculature, including possible hyperactivity of the parasympathetic nervous system, infections such as dysentery, and vitamin deficiency. Once the colon became spastic, it was potentially an organ capable of producing severe damage to its own surface structures. The exhaustion of the secretion of mucus, together with nutritional deficiency, might contribute to prevent healing of the colon. Muscular spasm might likewise be responsible for lesions of the mucosa of other portions of the gastro-intestinal tract as well.

W. C. Hunter.

*RHODAS, JONATHAN E., STENGEL, ALFRED, JR., RIEGEL, CECILIA, CAJORI, FLORIAN A. AND FRAZIER, WILLIAM D.

The Absorption of Protein Split Products from Chronic Isolated Colon Loops. Ann. J. Physiol., 125(4):707-712, 1939.

Isolated large bowel loops were prepared in dogs and the absorption of hydrolyzed peptone and of amino acid solutions, studied. A comparison was made with absorption of similar solutions from a small bowel loop. Amino acids were readily absorbed from chronic isolated loops of the large bowel. Some of the higher split products of protein digestion were apparently absorbed from such loops. Increasing amounts of total N and amino N in the large bowel loop resulted in increasing amounts absorbed in a given time. The rate of absorption of both types of substances was slower from the large than from the small bowel. The rate of absorption of amino N was more rapid from the protein hydrolysate than from the amino acid mixture.

J. E. Rhoads.

*GRAY, J. S. AND WIECZOROWSKI, E.

Development of Refractoriness to Enterogastrone Preparations. Proc. Soc. Exp. Biol. and Med., 40(3):324-326, 1939.

Preps. of enterogastrone, a duodenal chalone which inhibits gastric motility and secretion, induced a refractory state in certain dogs. Of 8 dogs with pouches (vagotomized) of the entire stomach that were repeatedly injected over long periods of time with enterogastrone preps., 2 became refractory within one month, whereas the remaining 6 dogs gave no indication of altered tolerance over periods varying from several months to several years. The tolerance was directed toward the impurities of the extracts, and not toward the chalone elaborated by the animal itself.

J. S. Gray.

*AUER, JOHN AND SEAGER, LLOYD D.

Auto-injection of the Biliary Passages From the Gall Bladder in Rabbit. Proc. Soc. Exp. Biol. and Med., 40(3):368-369, 1939.

Contraction of the gall bladder might drive its contents back into the biliary passages when the bile papilla was tonically contracted or when the choledochus was clamped. This was demonstrated in rabbits, narcotized with Na barbital, after 1 cc. of gall bladder-bile had been replaced by 0.5 cc. of 5% Na fluoresceinate soln. Contraction of the gall bladder was produced by the intraven. inj. of 0.5 cc. crude secretin soln. per Kg. The inj. of the liver was irregular and was most marked in the left ant. and left post. lobes.

J. Auer.

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*Amer. J. Digestive Diseases, Vol. 5, No. 6, p. 348, August, 1938.

**J. Lab. and Clin. Med., 19:567, 1934.

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*LIUM, ROLF AND PORTER, JOSEPH.

Etiology of Ulcerative Colitis. I. The Preparation, Care and Secretions of Colonic Explants in Dogs. Arch. Internal Med., 63(2):201-209, 4 figs., 1939.

Colonic explants made by the method of Drury, Florey and Florey; (by removing a segment of transverse colon with its mesenteric pedicle, suturing the abdominal wall loosely about the pedicle, denuding an area of skin, sewing the opened segment of colon to the margins of the wound on the surface) healed well and behaved as normal bowel wall so long as it was protected by dressings. The secretion of mucus by grafts when dressed daily was remarkably constant and was little influenced by the digestion of food or by starvation; dehydration, however, greatly diminished the amount of secretion. Mucus secretion was largely a response to the initial mechanical stimulation of the dressing and associated with muscular contraction. Once a layer of mucus formed on the dressing it protected the graft from further stimulation. The dominant effect of irritation caused by the dressing in inducing muscular contraction and secretion of mucus probably explained the failure to observe increases in secretion brought about by normal reflex muscular activity, as observed by Larson and Bargen.

W. C. Hunter.

*BACHRACH, W. H., SCHMIDT, C. R. AND BEAZELL, J. M.

The Relation of Bile and Pancreatic Juice to Duodenal Ulcer in Dogs. Proc. Soc. Exp. Biol. and Med., 40(3):322-324, 1939.

In a group of 15 biliary fistula dogs receiving bile by mouth or through a tube into the intestine there were only 2 cases of duodenal ulcer during a period of from 16 to 175 days. One instance of duodenal ulcer was observed in a series of 19 dogs surviving 21 to 720 days after separation of the pancreas from the duodenum.

W. H. Bachrach.

*BARRON, LOUIS E.

The Influence of the Splanchnic Innervation on the Motility of the Human Stomach. Rev. Gastroenterol., 6(2):109-114, 1939.

The splanchnic nerves may exert both an inhibitory and a motor influence on the stomach, but in general their effect is predominantly inhibitory. Resection of the splanchnic nerves in man removes this inhibitory influence, placing the stomach under the unopposed action of the vagus nerves. As a result there is a marked increase in gastric peristalsis, and

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PEPTIC ULCER

"Statistics . . show . . gastritis as a common complicating factor in duodenal ulcer."

Eusterman; Year Book of General Medicine, 1938, page 690

In a recent study of fifty cases of chronic superficial gastritis diagnosed by means of the gastroscope, a syndrome of duodenal ulcer was present in 26% of the fifty cases. (Bank & Renshaw, J.A.M.A., Jan. 21, 1939, pp. 214-217.)

Eusterman, Faber, Freeman, Taylor and many other authorities suggest a relationship between gastritis and peptic ulcer. Clinical evidence is plentiful that gastritis is a frequent accompaniment of peptic ulcer if not an actual antecedent of it.

So similar are the syndromes of these two frequently intermingled conditions that it is often difficult to differentiate between them. Treatment of each is in many respects similar, and should encompass the alleviation of pain and dis-

tress, reduction of gastric acidity when present, protection of inflamed mucosa, counteraction of inflammatory processes, and control of hyperperistalsis and pylorospasm.

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The acid-fixing action of CREAMALIN is profound, and in contrast to the fleeting action of the alkalis, is sustained. It usually affords prompt and continuous relief from pain and frequently induces healing even in stubborn cases where other types of therapy have failed. Unlike the alkalis, it provokes no secondary rise of HCl, does not disturb the acid-base balance, and therefore cannot cause alkalosis.

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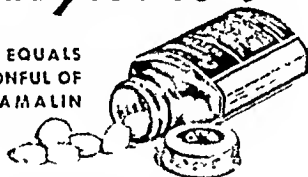
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48 cc N/10 HCl within 30 minutes (Toepfer's reagent). In contrast to the alkalis this antacid action is sustained.

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No Secondary Rise in HCl. No increase in HCl secretion is stimulated as is the case with the alkalis.

the emptying time of the stomach is shortened.

From auth. summ.

*ALTHAUSEN, T. L., ANDERSON, E. M. AND STOCKHOLM, M.

Effect of Adrenalectomy and of NaCl on Intestinal Absorption of Dextrose. *Proc. Soc. Exp. Biol. and Med.*, 40(3):342-344, 1939.

Rats which were adrenalectomized 5 days previously showed marked impairment in the intestinal absorption of dextrose. If the rats were allowed 1% NaCl in the drinking water during the post-operative period the intestinal absorption of dextrose was restored to normal.

Authors.

*CLARK, WILLIAM G.

Effect of Adrenalectomy Upon Intestinal Absorption of Sodium Chloride. *Proc. Soc. Exp. Biol. and Med.*, 40(3):468-470, 1939.

Healthy, adrenalectomized rats absorbed NaCl from the intestine at a lower rate than control rats. Another study revealed that no such decrease occurred in the case of glucose absorption. The methods used in the present study were both the Cori method (correcting for tissue NaCl) and a new method of rinsing the intestine with isotonic sucrose. The rinsing was done in the etherized rat after a definite absorption time following feeding of NaCl to the intact rat by stomach tube, 3% NaCl was given (1 cc./sq. dec. body surface), and completely disappeared from the intestine within 90 mins. Stomachs were separately analyzed. A curve was given, showing residual, unabsorbed NaCl plotted against time after feeding. In all cases, the adrenalectomized animals absorbed at a much lower rate than controls. Adrenalectomy evidently affected intestinal membrane behavior toward electrolytes directly, and not indirectly by, e.g., a disturbance in some phosphorylating mechanism causing decreased sugar absorption.

W. G. Clark.

*KRAJEWSKI, FRANCISZEK.

Die Einwirkung des niedrigen Atmosphärendruckes und der Einatmung verschiedener Gas-mischungen auf die Sekretions-tätigkeit der Magendrüs-en. *Acta Biol. Exp. [Warsaw]* 12(1):66-69, 1938.

Expts. were reported on dogs with a Pnlov pouch, kept in chambers at atmospheric and at lowered pressures of air, of pure O₂, and of 10% CO₂ in O₂; under fasting conditions, receiving vegetable juices, and subcutan. histamine. Changes were reported qualitatively on the rate and amount of gastric secretion, total acidity, free

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HCl, mucous and albumin. Blood chlorides, alkali reserve, albumin and blood cell counts were reported for an atmospheric pressure of 307 mm. Hg. The author postulated a control by way of the autonomic nervous system in response to changes in blood gas tensions. J. C. Sabine.

*FORBES, J. C.

Studies on the Prevention of Liver Cirrhosis by the Subcutaneous Injection of Xanthine Containing Preparations. Jour. Pharmacol. and Exp. Therap., 65(3):287-293, 4 figs., 1939.

The development of liver cirrhosis

from intermittent exposure of rats to CCl₄ vapor over a period of 9 to 11 weeks was retarded in all cases and in the great majority of cases prevented by the subcut. inj. of xanthine, Na xanthine, or a crude liver prep. containing approximately 50% xanthine.

Auth. concl.

ORR, T. G. AND RUMOLD, M. J.

Experimental Pyloric and Jejunal Obstructions, etc. Arch. Surgery, 37(2):295-301, 1938.

Jejunal obstructions were produced 25 cms. below the ligament of Treitz

in dogs, and various materials fed. Six dogs receiving water ad lib lived an average period of 11-1/3 days, six dogs given 0.6% NaCl solution lived 26-1/6 days, while 12 dogs given 10% alcohol, or 10% alcohol with 0.6% NaCl solution, lived about 12 days. In a similar series of pyloric obstructions, the six animals receiving water lived 4-1/3 days, while those given 0.85% NaCl solution lived an average of 5 days. The last group showed a more marked rise of non-protein N than any other group. NaCl is thus absorbed from the upper jejunum and lengthens the survival period in jejunal obstruction; alcohol did not appreciably lengthen life; giving NaCl in pyloric obstruction produced a striking rise of non-protein N.—N.W.R. (Courtesy Biol. Abst.).

SVEC, FRANZ.

Zerstörbarkeit der Digitalissubstanzen im Magensaft. II. Der Einfluss der Digitalissubstanzen auf die Sekretion der Magensalzsäure. Arch. Exp. Path. u. Pharmacol., 189(5/6):600-605, 7 figs., 1938.

In normal humans therapeutic doses of digitalis principles elicited gastric secretion of HCl. In achlorhydria or hyponcidity it was not produced. In normals, digitalis usually produced less HCl than did caffeine. In hyperacidity patients it caused strong HCl secretion. There were no noteworthy differences in the effect of the various digitalis principles tested. —C. S. L. (Courtesy Biol. Abst.).

WRIGHT, R. D., ET AL.

The Secretion of the Colon of the Cat. Section A. Effects of Nerve Stimulation and Certain Drugs, by R. D. Wright and H. W. Florey. Section B. An Investigation of the Enzymes of the Juice. by M. A. Jennings. Quart. J. Exp. Physiol., 28(3):207-299, 6 figs., 1938.

Stimulation by faradic stimuli at the rate of 30 per sec. of the peripheral ends of the severed nervi erigentes of decerebrate cats causes a secretion of fluid by the colon. The distal half of the colon forms this fluid at an average rate of 5 cc. per hr. when stimulated for 25 secs. per min. Secretion by the colon can also be excited by stimulating the central end of one nervus erigens when the other is left intact. The rate of secretion is reduced by stimulating the nerves emanating from the inf. mesenteric ganglia at the same time as the nervi erigentes. Stimulation of these paravertebral sympathetic nerves alone does not excite any secretion by the colon. The administra-

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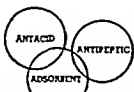
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tion of eserine increases greatly the rate of secretion excited by nervous stimulation. Narcotics, e.g., chloralose and luminal, greatly decrease the rate of secretion. This is a peripheral effect for it occurs in the completely decentralized colon. The fact that it is combated to a large extent by eserine suggests that it is due to narcosis of the enteric plexuses. A similar fluid is secreted in response to inj. of pilocarpine and, in the eserinated cat, acetyl-choline. Atropin inhibits the secretion caused by any of these procedures. The composition of the secretion is: total inorganic matter,

.95%; organic matter, .46 to 0%; Cl, .34%; Phosphate, 0.5 mg. %; Ca, 2.0 mg. %. Diptidase and a trace of amylase are present. This secretion is completely resorbed by the resting or atropinized colon. The reaction of the fluid when collected is about pH 8.4 but rapidly goes to pH 9.1 when exposed to the air. 1 cc. juice neutralizes about 0.5 cc. of N/10 HCl. The reaction of the solid faeces contained in the colon varies from pH 7 at the surface to as low as pH 4.8 at the center of the mass.—R. D. W. (Courtesy Biol. Abst.).

SOSKIN, SAMUEL, ESSEX, HIRAM E., HERRICK, J. F. AND MANN, FRANK C.

The Mechanism of Regulation of the Blood Sugar by the Liver. *Am. J. Physiol.*, 124(2):558-567, 1 fig., 1938.

The rate of blood flow through the liver and the arterial and venous components of the total hepatic blood flow were observed by means of the thermotromuhr in specially prepared dogs. The output or intake of sugar by the intact liver in situ was calculated in mgms. per min. by correlating the rates of blood flow with the simultaneously detd. content of blood sugar of the inflowing and outflowing blood. The movement of sugar out of, or into, the liver was observed during control periods and after the intraven. adm. of sugar. Prolonged constant injs. of dextrose as well as single large doses (dextrose tolerance tests) were used. During the control periods the liver was observed to secrete sugar into the blood. The adm. of dextrose was invariably followed by cessation of excretion of sugar by the liver and by retention of a portion of the incoming sugar. Inhibition of the output of sugar was observed in the absence of storage of sugar, following the adm. of certain smaller doses of sugar and at certain intervals after the adm. of large doses. At these times, the level of the animal's arterial blood sugar temporarily fell below the original control values and remained low until resumption of secretion of sugar by the liver restored it to its previous levels. Results yielded direct and quantitative evidence of the homeostatic regulation of the level of blood sugar by the liver, a mechanism for which only indirect evidence was previously available.—Auth. (Courtesy Biol. Abst.).

SELYE, HANS.

The Effect of the Alarm Reaction on the Absorption of Toxic Substances From the Gastro-Intestinal Tract. *J. Pharmacol. and Exp. Therap.*, 64(2):138-145, 1 fig., 1938.

Expts. show that substances such as adrenalin and histamine which are normally not absorbed to any great extent from the alimentary tract, readily enter the blood stream if they are introduced into the stomach during an alarm reaction caused by muscular exercise or exposure to cold. The increased absorption of toxic substances, such as are usually present in the alimentary tract probably plays an important part in the causation of the general damage re-

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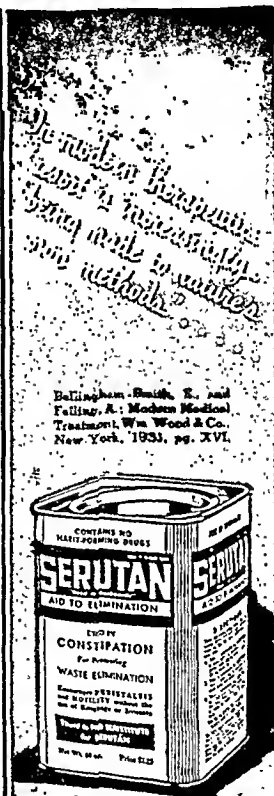
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● An adequate supply of food energy is one of a number of nutrient requirements of man. Fortunately, all nutrients—with the exception of water, minerals and accessory factors—supply chemical energy which the body can utilize to support muscular activity and life processes. Individual foods will, however, vary in the extent to which they supply food energy.

The energy requirements of man and the caloric values of foods have long been fields of active investigation. Energy requirements are measured in terms of a heat unit, the caloric. Many researches (1) show that human caloric requirements are variable and influenced by a number of factors.

During periods such as infancy, childhood, pregnancy and lactation, or during convalescence from wasting illness, energy-yielding nutrients are required both for support of body activity and for tissue formation. However, for the average adult, food energy intake should balance energy expenditure. For adults, variation in activity is the chief factor influencing variation in energy requirement; age, sex, size and body build being comparable. Sedentary occupations may require a food energy intake of 2500 calories per day; 5000 calories might be necessary if the individual engaged in strenuous muscular activity. Close approximations are available for the probable food energy requirements of individuals during different stages of the life cycle and engaged in various activities (1, 2).

Experiments (3) have also demonstrated that oxidation of foodstuffs in the animal body—due allowance being made for the energy contents of the end-products of oxidation—yields the same number of cal-

ories as are produced by the oxidation of similar foodstuffs in the combustion type calorimeter. Since the potential food energy of foodstuffs resides in their contents of carbohydrates, fats and proteins, the available calorific value of any food may be readily calculated (4) by using the factors 4, 9 and 4 calories per gram of these respective nutrients. Of these food components, the carbohydrates and fats are those which contribute most towards attainment of our varied, food energy requirements. Reliable tables are available (5) which list the caloric contributions of most common foods.

It has been established first, that foods—principally by virtue of their carbohydrate and fat contents—contribute energy for use by the human body; and second, that the human energy requirement is conditioned by many factors and may vary widely. An adequate supply of food energy is, of course, one of the necessary objectives of proper nutrition. However, individual attributes such as vitality, strength or endurance are influenced by—but not solely dependent on—proper nutrition, in which adequate food energy is supplied.

The food energy values of commercially canned foods are essentially those of the raw materials from which they are prepared. In some instances, the natural caloric values of the raw foods may have been enhanced by the medium in which they were packed, for example, carbohydrate-bearing syrups or sauces used in the canning procedure. Consequently, since canned foods include products of both high and low caloric intakes, such foods are valuable in formulating diets to supply any intake of food energy which might be desired.

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1. 1938. Nutrition Abstracts and Review. 7, 509.

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3. 1931. The Food and Nutrition Board of the National Research Council.

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1931. U. S. Dept. Agr. Circular No. 50.

1935. Dietetics for the Clinician, Second Edition, M. A. Bridges, Lea & Febiger, Philadelphia.

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sulting from various non-specific noxious agents. — Auth. (Courtesy Biol. Abst.).

DAVIS, CLARA L. AND FITZ-HUGH, THOMAS, JR.

Achlorhydria in the Leukemias.
Am. J. Med. Sci., pp. 763-766, June, 1939.

The authors studied 20 cases of myelogenous and lymphatic leukemia. 1, to investigate the incidence of true achlorhydria in leukemia; 2, to canvass the old concept of leukanemia of Leube in the light of Castle's conditioned deficiency hypothesis as follows: a, to find out if a pernicious

type of anemia occurs in association with leukemia, (i.e.) macrocytic anemia with glossitis, achlorhydria, and neurologic disturbances; b, to investigate the influence of liver extract therapy on such manifestations. Five cases exhibited achlorhydria with severe anemia and two other cases had achlorhydria without severe anemia. The alcohol test meal was used and histamine given if free acid was absent after the first hour. Of the five cases with severe anemia three showed a macrocytic type and two microcytic. These five cases were given parenteral liver therapy and in none was there any significant re-

ticulocyte response. Frequent blood studies were made during Roentgen-ray therapy. Tongue prints were made according to Middleton's method and there was no correlation between achlorhydria and smooth tongue. Smooth tongue was found in eight cases of the series. Roentgen-ray treatment was without influence upon the achlorhydria. Sore tongue was noted in one case.

Six necropsies were performed and leukemic infiltration of the liver was found in all cases, while infiltration of the stomach was found in only one and this patient had a normal gastric acidity during life. The authors compared the incidence of achlorhydria in their cases with the expected frequency in normal people according to the data of Bloomfield and Pollard and found it greater than normal.

Dobruff is cited by the authors as finding in 34 cases of myelogenous and lymphatic leukemia, acidity in more than one-half of the myelogenous cases and in less than one-quarter of the lymphatic cases. The authors' series did not reveal this type difference.

Regarding Leube's "Leukanemia" the authors find "no reality in the concept." Leukemia and pernicious anemia may exist coincidentally in an individual, as reported by Rich and Schiff, and the authors' observations agree with this. They conclude as follows:

1. Although too small for accurate statistical analysis, this series of 20 cases of leukemia exhibits an incidence of achlorhydria (35%) which is higher than the expected "normal."

2. There is no correlation between achlorhydria, glossitis, anemia and neurologic disturbances in this group.

3. Potent liver therapy has no effect on the associated anemia of leukemia.

4. The concept of leukanemia (Leube) is without demonstrable basis and the term should be dropped."

Allen Jones, Buffalo.

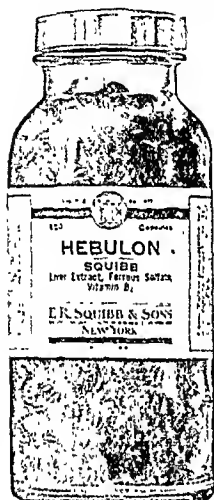
WIGODSKY, HERMAN S., RICHTER, OSCAR AND IVY, A. C.

The Presence of the Antipernicious Factor in an Extract of Foetal Bovine Livers. *Am. J. Med. Sci., pp. 750-754, June, 1939.*

According to Castle and his co-workers the gastric juice of pernicious anemia patients presenting achylia gastrica is deficient in some factor which is present in normal gastric juice.

The interaction of this intrinsic factor with some dietary principle termed an extrinsic factor produces a substance which is absorbed and stored in the liver.

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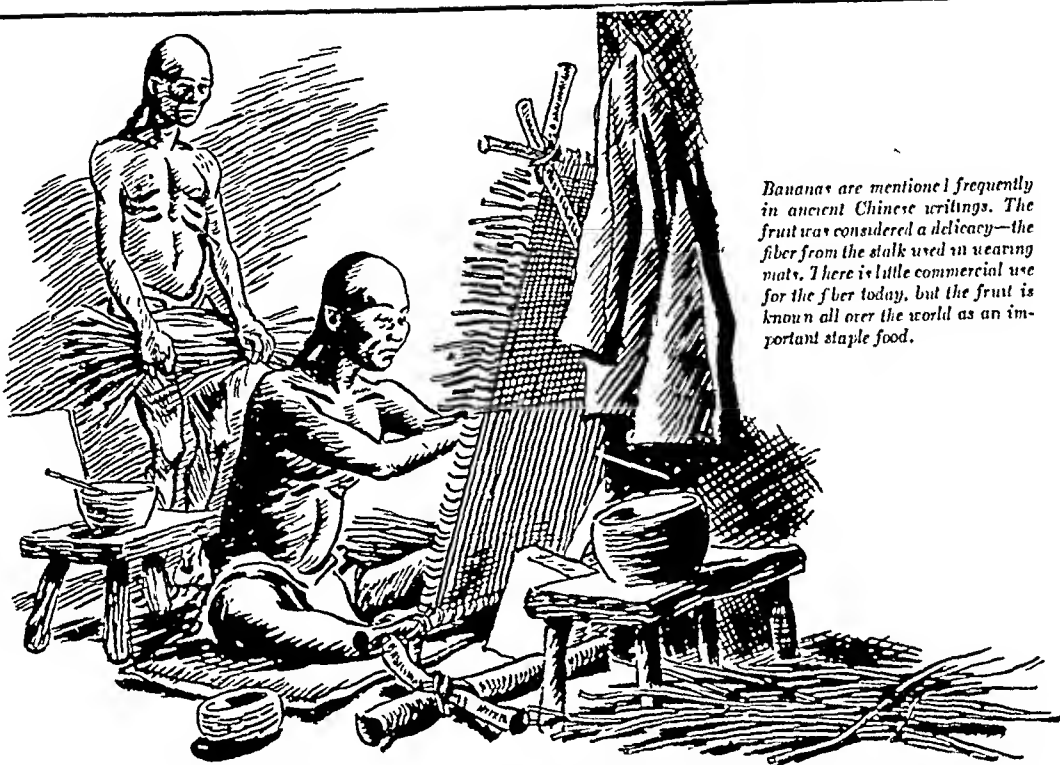
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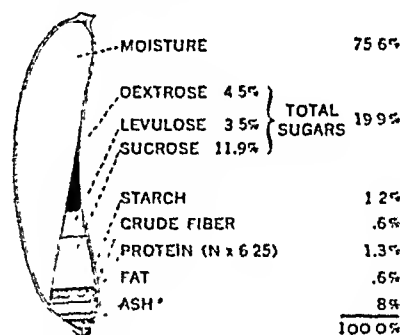
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result from (a) Lack of extrinsic factor in the diet; (b) lack of intrinsic factor in the gastric juice; (c) failure of absorption of the end product of the interaction of the above two factors. Goldhamer suggested two more means by which a macrocytic anemia might be produced; (d) inability of the liver to store the antipernicious anemia substance, and (e) inability of the bone marrow to utilize it.

The fetus lacks the extrinsic factor except for the amniotic fluid and the little detritus which collects in the intestinal tract. The fetus either must not require the liver factor or receives it from the mother through the placenta.

The purpose of the investigation was to determine whether the fetal liver contains the antipernicious anemia factor. Its presence in significant quantity indicates that the fetus requires the factor and that the mother produces extra quantities of the factor to provide for herself and the fetus. This would have significance in view of the fact that a macrocytic anemia sometimes accompanies pregnancy methods. An extract of fetal bovine livers was prepared by a method known to yield a potent extract when applied to livers of adult animals and three pernicious

anemia patients were treated with this extract.

Results: Case 1. A white female, aged 53, had been discharged from the hospital after being treated for pernicious anemia. She had not received liver since her discharge. She was in severe relapse and her r.b.c. count was 1,960,000 — w.b.c. 2400 — hemoglobin 46%. Intramuscular injections of 0.5 cc. of the experimental extract were given for 17 days, 0.5 cc. again on the 19th day, 2 cc. on the 20th day and 2 cc. weekly thereafter for two weeks. There was very marked improvement in her blood picture as well as subjectively. R.b.c. 4,270,000. W.b.c. 11,000. Hemoglobin, 79%.

Case 2. A colored female, aged 61, admitted to the hospital January 16, 1938, very ill with temperature 100.6° F., pulse 104, marked gastro-intestinal symptoms and no free acid after an Ewald test meal. The R.b.c. 1,110,000, W.b.c. 3800, Hgb. 25%. Intramuscular injections of 1.5 cc. of the experimental extract was given for 9 days, then every third day for five injections. At the end of this time, 3.6 cc. of a potent horse liver extract was given. Total of the experimental extract was 21 cc. Improvement was marked and at the time of the change from the experimental extract to the horse liver extract blood examination

revealed R.b.c. 4,090,000 — W.b.c. 4,400. Hgb. 65%.

Case 3. A white female, aged 68, admitted to the hospital February 6, 1938. She was an emaciated old woman with diarrhea, swollen feet, lemon yellow color and pale atrophic tongue. R.b.c. 1,360,000, W.b.c. 5600. Hgb. 34%. 1.5 cc. of the experimental extract was given daily for 13 days and 1.5 cc. on the 16th day. No more of the special extract was then available but at that time blood examination revealed R.b.c. 2,770,000, W.b.c. 4500. Hgb. 49%. Thereafter, a potent horse liver concentrate was given.

Prompt reticulocyte responses were observed together with return to normal blood pictures, indicating the presence of the antipernicious factor in the fetal bovine livers which may be most reasonably assumed to have passed from the placenta to the fetal liver since the fetus has no extrinsic factor. The authors searched the literature and found only four previous reports of the use of fetal liver in the treatment of pernicious anemia. The original article should be consulted for these references.

Allen Jones, Buffalo.

SCOTT, D. A. AND FISHER, A. M.

The Insulin and the Zinc Content of Normal and Diabetic Pancreas. *J. Clin. Invest.*, 17(6):725-728, 1938.

A series of normal and of diabetic pancreases were obtained at autopsy and the insulin and Zn content of each pancreas determined. In the pancreas of the diabetics the total amount of insulin present amounts to only $\frac{1}{4}$ that found in the pancreas of normal individuals. Likewise the amount of Zn contained in the pancreas of diabetics is only $\frac{1}{2}$ that normally present. There is no marked difference in the Zn conc. in livers of diabetics and non-diabetics. The possibility of a part of the Zn in the pancreas being concerned with the storage of insulin is suggested. — D.A.S. (Courtesy Biol. Abst.).

SARKADY, L. UND MARTIN, J.

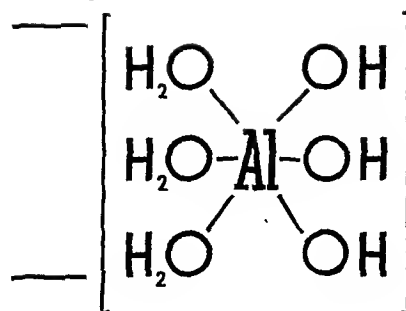
Vergleichende Leberfunktionsprüfungen an Eck-Fistelhunden. *Klin. Wochenschr.*, 17(37):1283-1286, 1938.

No histological changes were found in the liver parenchyma of Eck-fistula dogs, even after 11 months. The bilirubin functional test and the Takata reaction both showed functional disturbance; the galactose test of Bauer and the combined functional test of Althausen-Manche (insulin-glucose-water) showed less deviation from normal. Serum complement was lower. Erythrocyte sedimentation, fibrinogen content and Widal's hemoclastic test

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REPRINTS of the Editorial "Aids to Normal Bowel Function," *Amer. J. Dig. Dis.*, March, 1932; J. A. Bergen, M.D., will be supplied on request.

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were normal.—M.C.J. (Courtesy Biol. Abst.).

MONTGOMERY, M. LAURENCE.

Influence of Balloon Distention of Duodeno-Jejunal Loops on Volume of Combined Digestive Secretions. Proc. Soc. Exp. Biol. and Med., 39(2):352-355, 1932.

Dogs were prepared so that the combined digestive secretions were collected from a cannula in the upper jejunum. A Thiry-Vella fistula was formed of the bowel lying between. In 4 animals the fistula was denervated, in 7 the nerves were untouched. Respiratory and urinary fluid loss was controlled by salt solution injections. Fasting secretory levels were determined. Then a 200 cc. balloon was introduced into the fistula, distended suddenly with 50 cc. of water and gradually thereafter at the rate of from 6 to 8 cc. per hour. Animals with nerves to fistula intact showed an early abrupt fall in secretion which lasted from 12 to 24 hours. Those with denervated fistulae showed no such suppression. There was no hypersecretion. These findings are similar to those previously made on animals in which spontaneous distention of closed duodeno-jejunal intestinal loops was studied. — M. L. M. (Courtesy Biol. Abst.).

ALSTED, GUNNAR.

Exogenous Pernicious Anemia. Am. J. Med. Sci., p. 741, June, 1932.

Pernicious anemia may be regarded as due to a deficiency of antianemic factors which are intrinsic and extrinsic; the former being supplied by the pyloric glands of the stomach and the Brunner glands of the duodenum.

The antianemic factor is produced by an interaction between the two. The extrinsic factor is supplied by the food, meat, milk and eggs; and most amply by brewer's yeast and liver, in the latter with finished antianemic factor. Intrinsic factor can be conceived as an enzyme, while extrinsic factor seems to be related to the vitamins as it is frequently derived from the same sources as the Vitamin B₁₂ complex, yet it seems different from Vitamin B₁₂, lactoflavin and nicotinic acid.

True Addisonian anemia may be regarded as an endogenous condition, but several facts imply that the deficiency is more of a quantitative than of qualitative nature. Deficiency of finished antianemic factor with adequate production of intrinsic factor may explain the occurrence of pernicious anemia in some cases, when, for instance, there is lowered intestinal absorption as in idiopathic steatorrhea and intestinal strictures. In contrast, only sparse and partly uncertain information can be obtained

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*Further Clinical Observations on Feeding Infants Whole Milk, Gelatinized Milk, and Acidified Milk. C. Loring Joslin, M.D., F.A.A.P.; Bulletin of the School of Medicine, University of Maryland; Jan. 1939.

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on the anemic condition in which deficiency of antianemic factor is due exclusively to lack of "extrinsic factor," a condition which might be termed: exogenous pernicious anemia. The literature contains publications of pernicious anemia cases occurring with free hydrochloric acid in the stomach. The author, in 1934, collected all cases then in existence, and after excluding the majority of them, 32 were left; and to this number, he added 2 cases of his own. Some of these cases might have been leukosis, or idiopathic steatorrhea instead of true pernicious anemia. In two of the author's cases, it was established by most critical and exhaustive clinical and laboratory investigations and by meticulous follow-up observations and studies, that the disease was properly regarded as of extrinsic factor deficiency. (Richard A. Kern's study, published in the *Ann. Int. Med.*, 5, 729, 1931, suggested from clinical evidence that "in rare instances," an Addisonian type of blood picture may result in a patient whose diet is deficient in the extrinsic factor). The average daily intake of vitamins, calcium and phosphorus was carefully estimated before dietary treatment was instituted, and was found deficient in Vitamins B and C, as well as in calcium and phosphorus. The patient was given a plentiful supply of ordinary food, together with "extrinsic factor," which consisted of liver residue, as, the author says, they, at that time, had a preparation of that sort which in three cases of untreated pernicious anemia was shown to contain plenty of extrinsic factor, but no finished antianemic factor at all. This preparation was used from July 12th to August 14th (10 gms. 3 times daily with meals). A typical reticulocyte response set in, and during the following month, the anemia showed a complete remission. Gastric acidity was returned to normal, whereas, before treatment, anaemia, refractory to histamin, had been present.

The author's Summary is as follows:

A case of pernicious anemia is reported in a man of 43. It is shown that the development of anemia was due to deficiency of "extrinsic factor," continuous during 7 to 8 years. Treatment with "extrinsic factor" exclusively was followed by complete recovery and complete restoration of acid secretion in the stomach. The patient was controlled during 7 months, subsequent to the discontinuation of the specific treatment, and no relapse was observed.

The case is conceived as a case of exogenous pernicious anemia; its etiology and pathogenesis are discussed, as well as its relation to true endogenous pernicious anemia.

Allen Jones, Buffalo, N. Y.

ADLERSBERG, DAVID AND WEINGARTEN, MICHAEL.

Non-Granulomatous Chronic Enteritis. Ann. Int. Med., Vol. 12, 9, 1486, March, 1939.

The authors describe the clinical and roentgenological signs of non-granulomatous chronic enteritis. This condition is not easily to diagnose as practically all clinical signs are vague and could be also due to many different conditions. The authors stress the importance of the presence of fatty acids and soaps in the stools.

Roentgenologically Adlersberg and Weingarten distinguish between hypermotile and hypomotile cases. The hypomotile cases have apparently some relation to vitamin deficiency and are frequently found after a period of dieting. The authors report good results after parenteral liver administration.

Franz J. Lust, New York, N. Y.

GOTTLIEB, CHARLES AND ALPERT, SAMUEL.

Regional Jejunitis. Am. J. Roent. and Radium Therapy, 38, 6, 881, 1937.

Gottlieb and Alpert report a rare case of regional jejunitis which was confirmed by operation. The clinical signs were: severe epigastric pains, vomiting, bleeding from the gastrointestinal tract, fever and mild leukocytosis. The roentgenological findings were: duodenal distention, gross irregularity in the filling of the upper coils of the jejunum and flecks of barium after six hours in the diseased area. At operation this part of the jejunum was found to be very red, and thickened. The enlarged lymph nodes were succulent and showed hyperplastic lymphadenitis. The patient recovered and was later on free of symptoms.

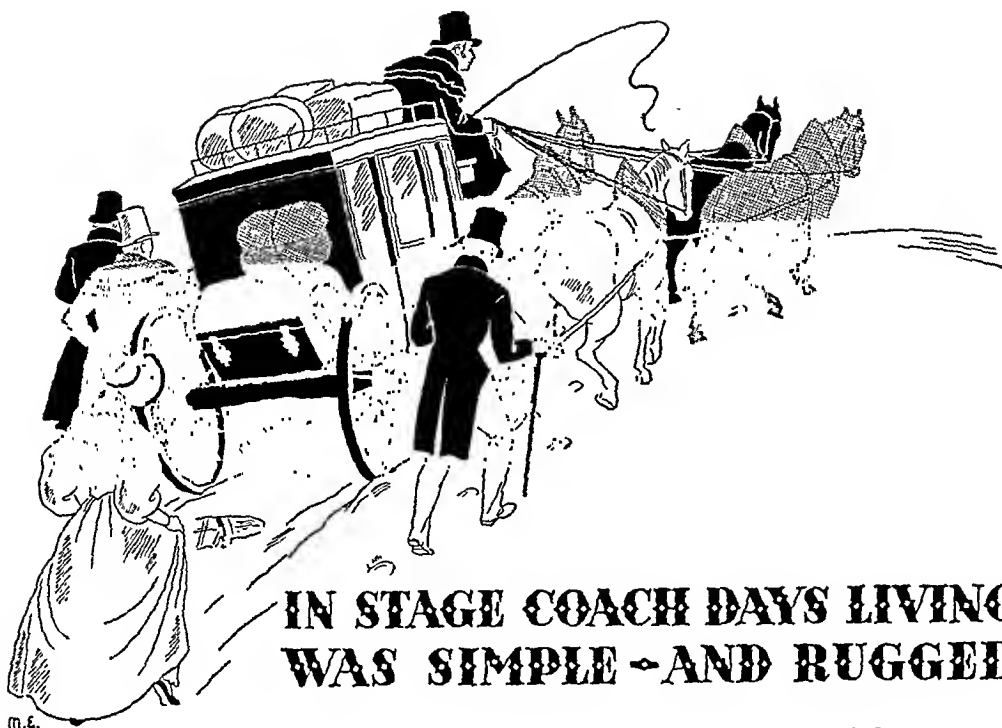
Franz J. Lust, New York, N. Y.

KANTOR, JOHN L.

The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions. Am. J. Roent. and Radium Therapy, Vol. XLI, 5, 758-777, May, 1939.

Kantor reports six cases of idiopathic steatorrhea. He found characteristic roentgen changes in the small intestines, colon, gall bladder and bony skeleton. These findings, however, were not constant nor all present in every case but varied in their degree and distribution depending on the activity of the disease and the constitution of the individual.

The changes in the small intestine were more apparent in the jejunum and consisted of variations in tone, caliber and motility, and particularly in the diminution or complete disappearance of the distinctive valvula conniventes. Kantor suggests the term "moulage sign" for the striking



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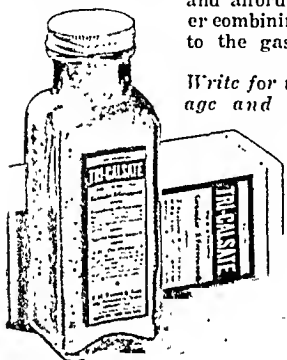
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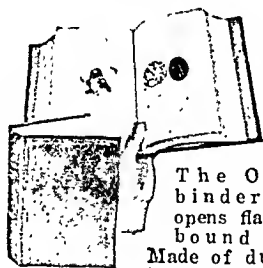
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appearance of the upper jejunum when the valvulae conniventes are missing and the lumen is filled smoothly as though wax had been poured into it. Since this peculiar appearance seems to vary directly with the intensity of the steatorrhea, the "moulage sign" may have practical value in both diagnosis and prognosis. The characteristic findings in the colon were marked dilatation, often associated with redundancy. The gall bladder showed only faint filling.

The pathological findings in the bony skeleton consisted of dwarfism, deformity and osteoporosis.

Franz J. Lust, New York, N. Y.

BARGEN, ARNOLD AND JACKMAN, RAYMOND J.

The Influence of Papaverine on Muscular Tone of the Intestinal Tract. S. G. O., 68, 740, April, 1939.

Bargen and Jackman used cases with a colostomy for their studies of pantopon, codeine and papaverine on the tone of the intestinal tract. They found that morphine and pantopon acted much alike, that the latter's sedative effect is probably due to its contents of papaverine. The action of codeine on the bowel was less striking. Papaverine caused not a constant decrease in tone of the intestinal muscle. However, an increase of tone was never observed. Papaverine compound (spasmalgin) had a striking effect in decreasing the tone and immobilising the bowel. Bargen and Jackman stress the high clinical value of this product.

Franz J. Lust, New York, N. Y.

JOHNSON, VICTOR AND FREEMAN, WILLARD.

The Adaptive Value of Absorption of Fats Into the Lymphatics. Am. J. Physiol., 124(2):466-469, 1938.

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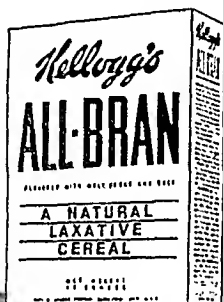
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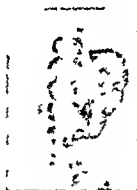
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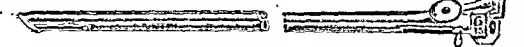
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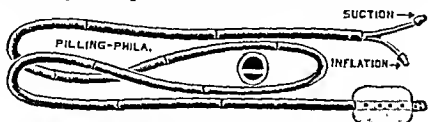
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Presidential Address, American Gastro-Enterological Association, 1939

By

ERNEST H. GAITHER, M.D.
BALTIMORE, MARYLAND

AS a prelude to this brief address I wish to express the deep and sincere appreciation I entertain toward you, my confreres, for the signal honor you have conferred upon me in elevating me to this very high office. I shall always remember my incumbency of this exalted position with heartfelt gratitude.

The more I consider the past, present, and future of the American Gastro-Enterological Association, the greater grows my conviction that ours is an organization with a distinct aim from which we should not swerve.

In this carpingly critical world of ferment we are at times challenged as to our course and practices, and feel that we must needs take up the gloves in our own behalf. However, it is well to pause first for a calm survey of the situation in all phases. If we do this, we shall immediately discover that no retaliation is necessary, and certainly no defense. Our Association occupies its own special and important niche in the medical fraternity; this foothold we shall maintain without the slightest deviation from our main objective, which is ever-increasing knowledge as to prevention, alleviation and cure of diseases in the digestive domain.

Whether at this stage of our careers we regret our present status as internists especially interested in the solving of problems regarding abdominal disease—so-called gastro-enterologists, a name upon which I do not look with particular favor—the fact remains that as internists in the broad sense we decided to project our energies forward in the field of abdominal disease and interpretation of intra-abdominal symptoms. In many instances these intra-abdominal symptoms are due to disease elsewhere, which means that if we are to develop into competent interpreters of symptoms related to the abdominal area, it is imperative that first and foremost we must be skilled internists.

I should like to dwell upon this latter problem for a few moments. There is no gainsaying the fact that during the past decade there has been in all too many instances an inadequate term of medical practice following graduation, and then an excessively rapid metamorphosis into a state of so-called "specialism," or in business parlance, expertism along special lines. The consequence has been just what one would expect. Immature and inadequately prepared practitioners who have not had the vitally necessary thorough training in the fundamentals of general medicine, have been foisted upon the public. Because of their callowness and lack of proper approach, they are not capable of qualifying as specialists or experts in the domain of diagnosis and therapy of abdominal disease, and further, their ineptitude, incompetency and ignorance have brought into disrepute medicine in general, as well as the specialty in which we are particularly interested.

It is just such organizations as ours that should assume leadership in arousing public sentiment in this regard. An excellent beginning in this direction has

been the establishment of the American Board of Internal Medicine, and to this agency we should in full measure declare our allegiance.

It is my opinion that at the earliest moment there should be set up a proper certification board relating to gastro-enterology, which would certify only those who had previously been licensed by the Board on Internal Medicine. Thus would be confirmed the integrity of the medical profession in general, and our specialty in particular, in our protestations to the public that we are anxious to protect them from the fads and schemes of charlatans, quacks, and incompetent, inadequately prepared members of the medical profession. In so doing, I feel assured that we shall not only earn the respect of the profession and the laity, but also increase our own self-respect.

It is no more than our duty to act in an unselfish and broadminded manner for the protection of those who place their health and lives in our hands and those of our medical confreres; to do less than this would to my mind constitute the betrayal of a sacred trust.

I now desire to take counsel with you regarding what I think a most important subject; that is, the limitations of our chosen field. Is there one among us who has not at some time thought in secret or said openly, "I am heartily sick, tired, and completely fed up on hearing about diseases of the liver, gall bladder, stomach, duodenum, pancreas, intestine, and all that pertains thereto?" In short, we do evince boredom at listening to the accepted and only diseases which we as individuals and as an association find of particular interest. I regret the necessity of confessing to you that I am one with you in this regard. In recent months, and after mature deliberation, I am convinced that such an attitude is not conducive to a furtherance of the work to which we have dedicated our efforts, so we must discard it and renew our enthusiasm.

If we consider our own field very limited and devoid of continuing interest, what would be our attitude if we were engaged in diseases of the nose and throat, eye, cardiology, pulmonary diseases, genito-urinary tract, gynecology and all other domains of the body which have been molded into circumscribed specialties! Yet those men and women continue to be interested, meeting year after year, and apparently finding ample stimulation to greater efforts in an attempt to further their knowledge in their accepted field. Will one of you deny that our specialty possesses far greater problems and potentialities than any of those just named? Why, one organ, and one only, the liver, offers a problem which has baffled and continues to baffle the keenest minds of our most gifted and brilliant scientists. Let us therefore lay aside the tendency to boredom with disease of the organs and areas to which we have devoted so much time, and develop, rather, a

more intense thirst for knowledge whereby we may solve the innumerable problems which confront us in every moment of our professional activity.

Let us now turn to a problem which has given us much food for thought; indeed, it has constituted one of the reasons for changing our constitution and by-laws. I refer to our past custom of not admitting to our membership anyone who has not published several or more papers of at least moderately outstanding merit. Even in an organization such as this, devoted to scientific investigation, I think we can go too far in barring everyone who has not shown a tendency to be fairly prolific in writing. I would like to be recorded with those who do not subscribe to the dictum "publish or perish," for it is my candid opinion that such an organization as ours will not flourish if nourished only on cold, scientific, albeit enlightening facts. Rather should we encourage and harbor in the Association, together with our scientific attainments, true friendship and cordial social interchange, striving at all times to discourage and eliminate all petty jealousies; this would further the growth of an atmosphere of true culture, which, after all is said and done, constitutes a combination of scientific accomplishment, sincere fellowship—mellowed and thoroughly ripened by true friendliness—and an earnest and ever-present

desire to render service one to another. I do not by any means wish to convey the idea that everyone who is sociable, attractive, and engaged in abdominal diagnosis should be forthwith admitted to our Association; but rather I am referring to the man—and you and I know of such instances—who is possessed of broad knowledge, is looked upon with marked respect by his colleagues, has readily advanced medicine because of his outstanding ability, accomplishments and inspiring character, and has as his only fallibility a failure to write; I do say that on occasion, and this may be rare, such an individual should not be barred from this organization.

In conclusion then, my sermonette consists of a plea for unity of purpose, high ideals, sincere companionship and solidarity in our organization, the furtherance of culture in order that we ourselves may increase in stature mentally, morally, and spiritually; and last, but not least, the continued amassing of knowledge.

Untiring research, wider learning, deeper understanding, will enhance our ability to prevent disease, or so skillfully to treat or to cure it that we may fulfil the great objective of our Association by proving our beloved profession an unselfish, tireless benefactor of suffering humanity.

The Clinical Significance of the Carrier State in Amoebiasis

By

JOHN TILDEN HOWARD, M.D.

BALTIMORE, MARYLAND

SINCE the Chicago epidemic of amoebic dysentery, amoebiasis in its various forms has been recognized clinically with increasing frequency in all parts of the United States. Whether *Endamoeba histolytica* has been disseminated from many foci originally seeded by visitors to the Chicago World's Fair, whether an ever increasing travel by our countrymen in tropical and sub-tropical countries has brought more of it home, or whether the Chicago epidemic simply increased our awareness of amoebiasis and stimulated our searches for the parasite, one cannot definitely say. Probably all these factors have played roles in the increase of infection or of the recognition of infection with *E. histolytica*.

Most of the persons who harbor the parasite have no striking diarrhea or dysentery; they are "carriers" and able technicians are constantly confounding such clinical diagnoses as Psychoneurosis, Congenital Fragility with Unstable Colon, Spastic Constipation, Chronic Appendicitis, Cathartic Colitis, et cetera, when they report the presence of *E. histolytica* in the stools. Much of the literature on the subject of symptoms in carriers of *E. histolytica* is contradictory and statements are too seldom supported by careful studies. On the one hand, Craig (1) stated that, in his experience, "About 65 per cent of carriers had symptoms referable to their infection, and these symptoms disappeared after the elimination of the parasite." And he said further, "Practically every untreated carrier of this

parasite either has, or will have, symptoms of the infection, unless spontaneous recovery occurs." On the other hand, Paulson and Andrews (2) in a recent study of 15 carriers with vague gastro-intestinal symptoms other than diarrhea, found no relationship between cure of the carrier condition and the relief of symptoms. Because of these and other varying opinions about the relation of the carrier state to clinical symptoms, the following studies were made.

What is the carrier state of amoebiasis? Every writer on the subject either avoids defining it, presumes that the reader understands the term, or has his own definition. Some would include under the term "carriers" only cyst-dispensers who never have a loose stool. Craig (3) accepts as carriers "Those who harbor the parasite without any appreciable symptoms of the infection, the so-called 'healthy carriers,'" and "Those who present indefinite and slight symptoms connected with the gastro-intestinal or the nervous system and who are also usually considered as healthy carriers." The definition of Craig was used in this study. As Table II shows, most of the carriers here reported had some abnormality in bowel function.

It would seem likely that the extent of the pathological lesions in the carrier state might give an adequate basis for clinical symptoms. However, such is not the case and the pathological picture in carriers is most variable. Hegner (4), infected four monkeys with *E. histolytica* obtained from human cases of dysentery. These animals showed no objective symptoms of their infection and were believed to be true carriers.

When they were killed, no lesions could be found in the bowel with the aid of a hand lens and sections of the bowel at different levels showed no pathology. With from 5 to 10 per cent of the population infected with *E. histolytica*, it is strange that more amoebic lesions are not found in the bowel at routine autopsies. MacCallum (5) says they are practically never found at routine necropsy, and he suggests that they may be overlooked by busy pathologists.

Craig (6) has collected a great deal of evidence to show that *E. histolytica* is a true tissue parasite and that carriers all have lesions of greater or lesser extent in the bowel; in that view he is supported by others (7, 8). James and Deeks (9), however, believe that *E. histolytica* "takes on pathogenicity only when it invades the tissues which is by no means a constant happening." Andrews and Atchley (10) point out that *E. histolytica* is not an obligate parasite for, in its artificial cultivation, it can multiply on a medium free from blood cells and serum and, in such a medium, it does ingest starch. These workers studied the pathology of carriers in an indirect manner. They reasoned that even minute lesions in the colon would ooze a little blood and they tested the stools of carriers of *E. histolytica* for occult blood by means of the benzidine test. In 12 of 13 cases examined the test was negative.

TABLE I
Clinical first impressions in 19 carriers

Psychoneurosis with unstable colon	6 cases
Unstable colon, cause unknown	5 cases
Questionable gall bladder disease	3 cases
Questionable appendicitis	2 cases
Fatigue with unstable colon	2 cases
Migraine with irritable gastro-intestinal tract	1 case
	19 cases

From this and other contradictory evidence, one can only conclude that the pathology of the carrier state of amoebiasis varies from an absence of lesions to very definite ulcerations of the colonic mucosa; the pathology is too variable to be used as a universal explanation of the gastro-intestinal symptoms of carriers.

Since we have rather specific weapons for the eradication of amoebae, probably the best approach to the problem of the relation of abdominal symptoms in carriers to their amoebiasis is the therapeutic test. If carriers are made well for a long period solely by amoebic sterilization, the amoebae may be presumed to have been the cause of the symptoms. The carriers here reported were 22 in number, 16 men and 6 women, between the ages of 22 and 75, who had abdominal complaints other than frank diarrhea or dysentery, who had no other intra-abdominal disease or important extra-abdominal ailment, and who could be satisfactorily followed after treatment. Carriers of "small race" *E. histolytica* were excluded. The symptoms in all cases were severe enough to make the patients consult their doctors or to make them go to a hospital dispensary. Eight of the patients were seen in the Out-Patient Department of the Johns Hopkins Hospital; the other 14 were private patients of Dr. T. R. Brown, Dr. E. H. Gaither, or of mine. They were

all given routine gastro-intestinal examinations which included a complete physical examination, blood count, serological test for syphilis, gastric analysis after an Ewald test-meal, fluoroscopic examination after the administration of barium sulphate (with films and with a Graham gall bladder series when either was indicated), and, of course, proctoscopic examinations and stool studies. In all but 3 of the cases an initial impression was recorded after the physical examination was completed and amoebiasis was in no case placed first in the list of possibilities. The preliminary

TABLE II
Symptoms of 22 carriers

Symptoms	Before Treatment	Within One Month After Starting Treatment	Three Months or More After Treatment
No data on bowel action		4	
Normal bowel action	2	6	7
Constipation	5	6	6
Slight diarrhea (including one mushy stool a day)	7	3	4
Alternating constipation and diarrhea	8	3	5
Gas on stomach	1		2
Gas on bowel	13	5	7
Mucus in stool	11	6	7
Pain in right lower quadrant	7	5	3
Pain in right upper quadrant and epigastrium	4	2	3
Pain in left lower quadrant	5	2	3
Pain in left upper quadrant	0		1
Cramps	3	1	2
Diffuse abdominal soreness	6	4	5
Acid stomach and eructation	1		1
Nervousness	14	6	15
Ease of fatigue	10	5	7
Aching of legs	1	1	1
Headache	4	2	3
Poor appetite	1		3
Nausea	4	2	3
Loss of weight	3	1	2
Somnolence	2	1	3
Undernutrition (objective)	5	5	3
	115	62	89

diagnoses are shown in Table I. As Table II shows, the most common symptoms were pain, nervousness, gas with the passage of flatus, mucus in the stool, alternating constipation and diarrhea, and unformed stools or slight diarrhea.

Each of the patients was given amoebicidal therapy according to the custom of his doctor. Nine were given emetine, Carbarsone, and chiniofon (the latter by retention enemata) simultaneously. One of the cases so treated required a second course. The others were given Carbarsone in doses of 0.15 gm. per kilo

in a ten day period as advised by Hakansson (11). Of the latter group, one required a second course of Carbarsone four weeks after the completion of the initial treatment. There were no drug reactions in either group. Faecal specimens passed without purgation and after purgation were examined at irregular intervals and, except as noted, no *E. histolytica* were found after treatment. At least three specimens were studied in each case three or more months after treatment had been completed. In most of the cases stools were studied more frequently.

During treatment (which necessarily included relative rest and which probably included a little suggestion) and directly after treatment all but 3 patients felt subjectively improved. The three who were not improved were neurotic, poorly adjusted women. Both patients who were not rid of their amoebae by the first course of treatment said that they felt better after the ineffective therapy. The second column of Table II shows initial improvement in the symptoms but it does not really show the clinical pictures. Totalling symptoms in this way is like adding the season's scores of the home team and comparing the result with the sum of the scores of opponents. Such a process reveals the situation in a general way but it gives no information about the games which were won or lost. However, with the exception of the three women mentioned, the patients were much better directly after treatment; on persistent questioning the symptoms charted were obtained.

Three months and longer after the eradication of amoebae and with the stools still microscopically negative for *E. histolytica*, only 6 (27 per cent) of the 22 carriers considered themselves to be strikingly better or to be digestively well as the result of treatment. The original symptoms of all 6 of the cured or practically cured patients had caused them to be classified in the group of unstable colons at the time of their first examinations. Nine of the 15 carriers, who continued to complain, were given bromide or phenobarbital, a smooth diet, anti-spasmodics, and directions for colon management. Seven of the 9 so treated were improved with this type of therapy when amoebicidal treatment alone had failed to give real improvement.

Paulson and Andrews (2) in a similar study of carriers found no correlation between the relief of symptoms and the eradication of amoebic infection. Of their 15 carriers, not one was relieved for a long period by anti-amoebic treatment alone. The difference in their report of no successes in relieving symptoms in 15 carriers and this report of 27 per cent therapeutic success in a group of 22 cases can probably be explained. All of the 6 patients in whom symptoms were relieved for three months or longer by amoebicidal therapy were cases with symptoms of an unstable colon, i.e., they had a mild mucous colitis or spastic colitis with constipation that would break into a slight transient looseness at times, flatulence, and some abdominal pain. Very strictly speaking, these patients might have been called cases of subclinical amoebic diarrhea. In the series of Paulson and Andrews no cases of bowel disturbance with any mushy stools (other than those following a laxative) were included; consequently they had no subclinical or near subclinical dysentery to treat.

It is well known that in chronic amoebic dysentery amoebic ulceration with secondary infection may pro-

duce over many years so much scarring and fibrous stiffening of the bowel wall that normal function is unlikely even after eradication of the amoebae (12). In the cases here reported the mildness of the symptoms makes it seem likely that any possible ulceration was not sufficiently extensive to have permanently injured the bowel function. Two of the patients treated successfully had had symptoms for 22 and 16 years. One has only to see the perfect recovery of a patient with frank amoebic dysentery of many months duration to feel that the scarring has to be most extensive to produce permanent dysfunction.

CONCLUSIONS

Twenty-two carriers of *E. histolytica*, who had abdominal symptoms and who had no organic condition, other than amoebiasis, which might have produced those symptoms, were given a therapeutic test.

(1) While 19 of the carriers were improved for a short time on the rest, suggestion, and "tonic effect" of therapy, only 6 (27 per cent) patients were freed from abdominal symptoms by the treatment when they were studied three months or longer after its completion. Amoebiasis should be looked for in all patients with gastro-intestinal complaints, but too striking clinical improvement should not be expected from the amoebicidal treatment of carriers. This statement is in contradiction to the usual teaching.

(2) All of the patients who were relieved of their abdominal complaints by treatment had complained in such a manner that their abdominal syndromes could be described clinically as those of "the unstable colon."

(3) Many of the patients, who were not relieved for a relatively long period by amoebicidal therapy, responded for a time to sedatives, bowel management, and antispasmodics.

All carriers of *E. histolytica* should be rid of their parasites for public health reasons and to avoid the possibility of later complications in the carriers themselves.

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DISCUSSION

DR. RALPH C. BROWN (Chicago): In connection with the question of amoeba histolytica carriers, attention should be called to the fact that in individuals who can be classified as the pure type of carriers, i.e. where there is no history whatever of bowel dysfunction, the gravest form of hepatitis—liver abscess—may occur.

As an illustration I recall the case of a forty-five year old executive who, while at his desk, was seized with a very severe chill. The temperature rose to 103° and it

was thought that he had paeumoain, but the physical findings were negative. The temperature declined somewhat in a day or two but he continued to have an evening temperature of 100.6° to 101° for six weeks. No subjective symptoms other than general malaise. In the meantime careful diagnostic work was done with negative results. He was under the care of an able physician. I saw him six weeks after the onset and was unable to discover the cause of the continued fever. I suggested stool cultures for amoeba histolytica which were made and reported negative. A week later he entered the Presbyterian Hospital on my service and on that day coughed up an appreciable amount of bright red blood. Physical examination negative. Leucocyte count 22,000. (Leucocyte count had ranged between 20,000 and 24,000 throughout the illness). Chest films revealed a dome-shaped elevation of the upper margin of the right lobe of the liver with penetration through the diaphragm and an inflammatory process already well established at the base of the right lung.

Within twenty-four hours of admission to the hospital stool cultures yielded a rich growth of amoeba histolytica and the pathology and symptoms disappeared with great rapidity on anti-amoebic treatment.

This was the third case of liver abscess due to the

amoeba histolytica we have observed in individuals who showed not the slightest evidence of bowel dysfunction.

DR. JOHN TILDEN HOWARD (Baltimore): I, of course, agree with Dr. Brown. All carriers should be rid of their infection because it is so simple to get rid of it and because it may give them trouble later on. The case to which he referred was not the classical type of case that we had. We had cases who had vague abdominal symptoms but had more chronic abdominal complaints. Of course, one would think that the pathology of the carrier might explain the symptoms but the pathology is so variable, from the absence of lesions to quite extensive lesions in the bowel, that the pathology doesn't help us very much.

Before I came here, I called Dr. MacCallum on the telephone and said, "Why don't you see lesions in the bowel in case out of every ten autopsies you do, if 10 per cent of the population is supposed to consist of carriers?"

He said that they rarely, if ever, found at routine autopsies, lesions in the bowel which were proved to be amoebic. Certainly that is not the idea that Dr. Craig would give us. Dr. MacCallum said that perhaps he didn't look for them hard enough. Be that as it may, it is quite uncommon to see lesions at routine necropsy and the pathology of the carrier doesn't help us in an explanation of the symptoms.

Perforation of the Colon Complicating Bacillary Dysentery

By

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THE rarity of perforation complicating bacillary dysentery justifies my bringing to your attention a small series of cases in which there was this unusual complication. Even in chronic bacillary dysentery, where ulcers have existed for many years, perforation is seldom seen. In the perusal of the literature I have been unable to find but two cases of perforation of the bowel in bacillary dysentery and it was in both acute fulminating and chronic types, reported by Duval and Kahn and by Craig.

Charles F. Craig (1), discussing complications of the amebic and specific types of dysentery as observed at autopsy, noted four instances out of 120 cases of perforation due to amebiasis, and only one of perforation due to the chronic specific form of dysentery. All of these cases resulted in death from peritonitis. P. Duval and P. Kahn (3) in 1908, reported one case of perforation of the colon complicating acute bacillary dysentery, the diagnosis being confirmed at autopsy.

Perforation in bacillary dysentery either as a complication or a sequela is as rare as perforation in intestinal amebiasis. In intestinal amebiasis the reason for perforation being unusual is the late invasion by secondary infection of an acute inflammatory nature. In amebiasis there is constant repair going on which gradually and surely thickens the bowel with cicatricial tissue. This cicatricial tissue renders the bowel more and more less likely to perfo-

rate. Further it is the acute inflammatory infection of the small bowel that is more likely to perforate. While bacillary dysentery is in itself an acute inflammation it is commonly so superficial that the likelihood of perforation is in consequence rarely encountered. Undoubtedly in chronic bacillary dysentery those cases that do perforate are those in which the acute inflammatory process has extended down through the muscular coat. Of course, perforation from either amebic or bacillary dysentery is extremely rare as compared with perforation in typhoid fever or other infections of the small bowel. The reason here is anatomical, the small bowel being much thinner than the large bowel. Then again perforation in large bowel infection is more often seen in the cecum and ascending colon than in the descending and sigmoid flexures. This is also because of anatomical reasons, the lower part of the colon being thicker than the upper part. Felsen (4), in his experience, had never seen a case of perforation of the colon in bacillary dysentery until recently when he saw two cases. C. Duval (2), the discoverer of the lactose fermenter, which was the cause of perforation in one of my cases states that he has not encountered a single case of perforation complicating bacillary dysentery.

It is because of the unusual occurrence of perforation in bacillary dysentery that I have deemed it of sufficient importance to bring before the profession my series of cases. Another reason for presenting these uncommon cases is that, clinically, the acute infection that undoubtedly precedes the bowel rupture in certain instances may have entirely subsided and

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the actual rupture due to bacillary infection go unrecognized. In this connection I wish to recall a case that was of this character and the attack was diagnosed acute appendicitis. In the acute fulminating cases that terminate by bowel rupture the latter is the result of thrombosis which subsequently leads to infarction of that part of the bowel wall supplied by the occluded vessel or vessels. The area or areas of infarction rapidly become invaded by microorganisms from the intestinal content. This invasion through microbic enzyme action causes a softening of the necrosed tissue. Now with the peristaltic action of the bowel there results a sloughing of the destroyed tissue. While this sloughing may only increase the depth of the ulcers later, however, through further infection at the bottom of the ulcer the tissues here will become weakened and destroyed which produces an area liable to rupture upon the slightest peristaltic movement.

M. H., a man of 21 years, was first seen in the office on June 18, 1931. He complained of a diarrhea of three weeks' duration. The stools were watery and of a mucous character, numbering four to eight per day and one to four each night. He suffered some pain, occasionally. He reported a similar attack one year previously, which he had attributed to eating oysters.

This patient was exceptionally well developed. A generalized abdominal tenderness was noticeable, particularly in the left iliac fossa. Examination of the stool showed numerous pus cells, but no protozoa. Proctoscopic examination revealed a moist and granular mucous membrane, with a few superficial ulcers. Agglutination of the blood serum was negative for *B. dysenteriae*, Hiss, Flexner and Shiga on June 23, 1931. Cultures of smears made from scrapings of the rectal mucous membrane, however, revealed the presence of *B. dysenteriae* Flexner-Harris; the blood serum from the patient showed a strongly positive agglutination with the strain of organism isolated from the intestine.

Hospitalization was advised on June 27, since the abdominal cramps, soreness and frequent stools had continued. Autogenous vaccine was administered. A high caloric, non-residue diet was ordered and the colon was irrigated daily with normal saline solution. The patient was discharged on July 18, after all symptoms had disappeared. Vaccine therapy was continued for three weeks after he left the hospital, at the end of which time inspection of the lower intestine showed no lesions.

On October 26 he returned to the office, complaining of severe pain in the right lower abdomen, which had begun the day before, and was increased on exertion. Examination disclosed a definitely localized tenderness over the cecal region but no rigidity. Blood examination showed total white cells 23,000 with 82 per cent neutrophils (segmented cells 79 per cent, of which there were three staffs). Subacute appendicitis was suspected and he returned to hospital on October 27. The consulting surgeon confirmed the tentative diagnosis. Operation revealed a normal appendix, but showed a subacute perforation of the cecum within one inch of the appendix. Recovery from the operation was uneventful. At this time tuberculin skin test was negative; blood serum was agglutinated against *B. dysenteriae*, Flexner and Hiss were negative as on previous examinations. The proctoscope revealed an inflamed and ulcerated lower intestine. No diarrhea was present, however, and cultures were negative for *B. dysenteriae* and positive for staphylococci, streptococci and *B. coli*. Two weeks after leaving hospital, agglutination with the vaccine which was autogenous, the Flexner-Harris strain was strongly positive, but negative against Shiga, Hiss Y. and Flexner bacilli. One week after leaving the hospital a barium enema examination showed filling of the entire colon, without evidence of abnormal filling defects.

The proctoscope at this time showed no rectal or sigmoidal ulcers.

The patient enjoyed normal health for a year. Returning in November, 1932, examination disclosed a marked tenderness in the right iliac fossa, where a small, tender mass was noted. The consulting surgeon believed that another rupture had taken place and that an abscess was forming. The patient was therefore hospitalized. The blood count showed 25,500 white cells, 81 per cent neutrophils. A second blood count showed 25,500 white cells and 74 per cent neutrophils. Operation on November 21 disclosed a fetid, pericecal abscess which was opened and drained. Cultures from the pus showed *B. coli*. The patient remained in hospital until February 11, 1933, with an irregular temperature, running at times to 100-101°. Barium enema examination at the present time shows a cecal fistula without visible pathology in the lower intestine, and normal filling of the entire colon except the cecum.

DISCUSSION

Here is an instance in which bacillary dysentery infection to all intents and purposes was cured. The patient had no fever or intestinal symptoms of any kind for several months. With this interval of well being and the sudden development of signs of bowel perforation and the subsequent finding following operation that this was due to the dysentery bacillus proves conclusively that the dysentery infection continued over the entire period. This case also illustrates that bacillary dysentery may exist for a comparatively long time without there being any clinical evidence. Of course the vaccine therapy that was originally instituted in this case may in part or whole be responsible for the disappearance of all clinical evidence of the infection, though the latter undoubtedly still existed. Other proof that the infection remained after the subsidence of all symptoms is substantiated by the presence of definite mucosal ulcer which were observed on proctoscopic examination following the operation. This case further illustrated that acute bacillary dysentery can become chronic, persisting for years without the patient being aware of his condition. In this respect there is a close analogy of chronic bacillary dysentery to intestinal amebiasis. In my opinion it is this type of case that is so often diagnosed clinically as amebic infection even though repeated examination of the stool fails to reveal the presence of ameba histolytica. Again I would like to point out that it is this type of case that is mistaken for amebiasis that fails to respond to the treatment for amebic infection.

H. V., a white man, 46 years old, entered hospital on April 18, 1937, complaining of severe pain in the abdomen. He reported having passed blood in frequent stools for ten days past. The abdominal pain was severe and generalized. He had lost considerable weight and suffered from malaise. The patient was very weak and somewhat delirious.

Examination showed the abdomen to be generally distended and very tender. Blood count showed 4,300,000 red blood cells; 85 per cent haemoglobin, 14,000 white blood cells. Proctoscopic examination revealed a diffuse inflammation and marked edema of the entire mucosa of the rectum and sigmoid. *B. Duval* isolated from the stool. A definite mass could be palpated in the right iliac fossa. Temperature was 103°. On April 20 the temperature rose to 106.4°. Blood count showed red blood cells 4,400,000, haemoglobin 85 per cent, white blood cells 22,000. Immediately following an infusion of 1,000 cc. of 5 per cent glucose and normal saline solution, the patient developed chills and marked hyperpyrexia with a drop in blood pressure from 130/65 to 80/40. An acute dilatation of the

heart was noted. The high temperature and increased leucocytosis led to a tentative diagnosis of rupture of the colon (cecum) with localized peritonitis due to perforation of a dysenteric ulcer. On April 22 the size of the heart had receded to normal, the blood pressure rising to 120/75. On the following day skin tests to *B. dysenteriae* were made, which signified the patient's hypersensitiveness to the *B. Duval*, producing his infection, even in high dilutions of vaccine. By May 1 red blood cells had increased to 5,400,000, haemoglobin 90 per cent and white cell count had decreased to 7,000. The patient was discharged on May 10, 1937.

DISCUSSION

In discussing the case of H. V., I wish first to say that the perforation was undoubtedly slow in occurring which gave time for the reacting peritoneum to localize the infection about the site of the perforation. Thus the resulting peritonitis was kept from becoming general. Perforation may complicate bacillary dysentery regardless of the offending strain of *B. dysenteriae*. In my series of cases of perforation this case was caused by the lactose fermenter. It might also be mentioned in this connection that the virulence of the infection is not necessarily the determining factor of perforation. This complication occurs no more frequently with the Shiga than with any other member of the dysentery group. Where perforation may occur or is suspected it is well to know at once the strain of dysentery organism that is concerned as treatment will depend in large measure on knowing the particular causal excitant. This applies equally where antitoxin or vaccine is indicated.

S. H., a white male, 71 years old, entered hospital on July 22, 1936, complaining of abdominal discomfort and diarrhea of three days' duration, in which gross blood was passed in considerable quantities. The patient reported frequent trips about the country, when he was accustomed to drinking water from almost any source. He was well developed and well nourished. Examination showed the abdomen to be greatly distended, as if with gas, and it was resonant to percussion. There was a generalized soreness, but no localized tenderness. Blood count showed red blood cells 5,000,000 haemoglobin 77.9 per cent, leukocytes 8,800. On July 27 the patient seemed more comfortable. The stool showed organisms with the cultural characteristics of *B. dysenteriae*, although this was unconfirmed by agglutination. The patient continued to improve during the following week, but the stool retained its original appearance. On August 12, 500 cc. of citrated blood were administered by direct transfusion. The patient complained of pain in the upper chest, his temperature rose to 103°. Drainings from the rectal tube were the color of mulberry juice. A second transfusion of 250 cc. of citrated blood and 100 cc. of saline solution was given on August 15, to be followed on August 18 by a third transfusion of 300 cc. of blood without immediate reaction. Autogenous vaccine was given intradermally. All skin reactions were negative. On August 21 the patient suffered severe rigor with marked cyanosis. The urine showed pus and bacteria, and a urinary antiseptic was given by vein. Transfusion of 500 cc. of citrated blood was followed by 500 cc. of ten per cent glucose without immediate reaction. Culture from the intestine revealed *B. Shiga*. On August 22 the patient presented diarrheal stools which were non-dysenteric in character. Palpation of the abdomen on August 23 showed a diffuse elongated mass which was smooth and suggestive of thickening of the sigmoid colon occasionally seen in chronic bacillary dysentery. Continuous drip blood transfusion was started (temperature 99.8°, pulse 100, respiration 22). On August 26 the Shiga bacillus isolated from the stool was shown to be the identical organism isolated from a catheterized specimen of urine,

both culturally and serologically. The patient was alert but cyanotic. Respiration was difficult. The congestion of the lungs was more marked and an overwhelming toxemia was evident. 950 cc. of five per cent glucose in saline was given; 100 cc. of calcium gluconate was administered with the glucose resulting in a distinct improvement. On August 27 several blood clots were passed by rectum. 60 cc. of antidysenteric serum plus 60 cc. of saline solution were administered intravenously. On the following day a large amount of blood mixed with fecal material was passed per rectum. This was followed by a chill and the passage of more blood. The pulse grew faster and weaker as there was further rectal hemorrhage. The patient died on August 29.

Autopsy showed the cecum distended with gas. The mucosa of the colon at the hepatic flexure revealed superficial ulcers with soft bases. The ulceration increased toward the splenic flexure, and in the sigmoid and rectum the mucosa was almost completely destroyed by the massive lesions. No diffuse peritonitis was present. Sections from the ulcerated colon showed extensive necrosis extending to the muscular coat in many places. No ameba could be demonstrated.

DISCUSSION

Concerning case of S. W. in which the patient was acutely ill from the onset of the infection until there was perforation it is evident that the infection was so severe that there was more than the usual mucosal involvement of an early case. The autopsy which was held on this case following the perforation showed every evidence that in places the entire bowel wall down to the serosa was involved. It was this early deep involvement of the bowel wall that led to the subsequent perforation. While fulminating types of acute bacillary dysentery that result in perforation are extremely rare, it is my opinion that the physician should always keep in mind this serious complication. Where perforation is considered a possibility every means should be taken to forestall it. As in the treatment of typhoid fever it becomes essential to withhold all solid foods and minimize peristalsis, feeding the patient parenterally for several days. Intravenous glucose solution for supplying fluid and food are indicated and blood transfusion is far the best procedure in these cases because it is an ideal way for supplying nutritives directly to the tissues.

N. H. T., a white salesman, 32 years old, reported his illness to have begun on November 15 after eating in a small country hotel; the attack had begun with abdominal cramps and diarrhea. He reported that two other persons had been similarly attacked at the same time. The patient was confined to bed for six days with a fever ranging as high as 104-105°. At the end of this time, since his condition was unimproved, and the number of stools undiminished, the patient returned to the city and was examined by his physician on November 21. In spite of treatment at home, the high fever, abdominal cramps and diarrhea continued, with occasional passage of fresh blood. Since he could take no nourishment, he became very weak and lost appreciable weight. He entered hospital on November 29 in a state of emaciation. On examination, a diffuse tenderness was apparent over the whole abdomen, more marked in the left lower quadrant. His temperature on entering hospital was 101°; pulse 108. There were frequent watery stools, but no gross blood. No ameba or ova were found in the stool. White blood cells, 8,750; polymorphonuclears 84 per cent. The patient's condition seemed to improve somewhat during the next several days. On December 2, white blood cells, 11,450; haemoglobin 75 per cent. A continuous drip of 5 per cent glucose was instituted, 4,000 cc. in 24 hours. On December 4, stool culture showed strepto-

cocci and *B. coli*. A large piece of mucosa sloughed off and was passed. Haemoglobin, red blood count and white blood count were diminished (red blood cells, 3,530,000; haemoglobin 70 per cent; white blood cells, 7,550). A marked tympanitis was noticeable. On December 7, 350 cc. of blood were given the patient by direct transfusion. Continuous glucose drip was again instituted. The patient grew weaker, and now with continual bloody stools. He died on December 9.

At autopsy, a large amount of foul smelling gas and about 3 liters of fluid were released, lying free in the abdominal cavity. The transverse colon was found to have ruptured over its entire length and the anterior surface or wall of the transverse colon formed one side of the lumen; while the posterior side was formed by the loops of the small intestine. Dense fibrous adhesions lateral to the cecum attached the latter organ to the wall of the abdomen. Above the terminal portion of the cecum was an ulcer, or perforated area, 3 cm. in diameter, in the wall of the ascending colon. Its edges were rough and irregular. An acute inflammatory peritonitis extended all over the abdominal cavity. The liver was markedly enlarged. Incision through the whole length of the colon showed it to be intensely ulcerated, the whole mucosa showing this acute inflammatory reaction with necrosis and inflammation.

Culture in blood broth of material obtained from lesions at autopsy showed streptococci and gram negative bacilli, which were identified as the Flexner strain of *B. dysenteriae* and was agglutinated with known Flexner serum in dilutions up to 1:320. No agglutination by known Shiga and Duval serum.

DISCUSSION

Perhaps the most interesting one of the cases of my series of perforation of the colon is the mixed amebic and bacillary infections. It is hard to determine whether the ameba or the specific bacillus of dysentery played the greater role. The microscopic sections would indicate, however, that the ameba, which appeared in large numbers, caused a chronic colitis and

that the superimposed acute illness was due to the dysentery bacillus.

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DISCUSSION

DR. JOSEPH FELSEN (New York): I shall confine my remarks to two important points of Dr. Silverman's paper. The first is the insidious nature of bacillary dysentery. Next to syphilis, bacillary dysentery is perhaps the greatest disease mimic of all time. This is illustrated by the atypical forms of acute bacillary dysentery such as the pneumonic type which simulates lobar pneumonia. I feel that probably the most logical concept of this disease is one that regards it as a focal intestinal manifestation of a systemic infection with toxin absorption. This corresponds to what Dr. Gaither meant, I presume, when he said that the bowel should be considered in relation to the other organs of the body.

The second point is the occurrence of perforation in bacillary dysentery. It is my humble opinion that intramural infection is a common accompaniment of both the acute and chronic forms of the disease. In the chronic form, multiple intramural abscesses may occur, giving rise to a septic type of temperature and a rather typical clinical picture of profound toxemia. These were evident in one or two of Dr. Silverman's cases. Intramural infection in bacillary dysentery follows the general distribution of the submucosal and muscular lymphatics of the bowel wall much the same as in tuberculosis or carcinoma. Perforation of an intramural abscess, however, is rare since a well defined zone of productive inflammation or fibrosis is formed on the serosal surface. This serves to wall off the area involved and, although signs of local peritoneal irritation may occur, frank perforation is the exception rather than the rule.

The Value of Peritoneoscopy in Gastro-Enterology*

A Review of 100 Cases

By

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EXAMINATION of the abdomen and pelvis by endoscopy was first demonstrated by Kelling (1) in 1901. He tried the procedure in dogs, and many years later practised it in human beings. In the meantime Jacobaeus (2), about 1910, published several papers on thoracoscopy and laparoscopy, concluding that the latter method was useful in cirrhosis, syphilis, metastatic tumors and tuberculous peritonitis. The recent revival of interest in the subject has been due largely to the work of Ruddock (3) who in 1937 reported 500 cases examined by peritoneoscopy. Other recent contributors to the subject include Anderson (4), Benedict (5), Findlay (6), Hope (7), Horan (8) and Thieme (9). Meigs (10, 11) believes the procedure is valuable in gynecology and Allen (12) has stressed its importance in abdominal surgery.

For a detailed description of the peritoneoscope, technic of introduction, indications and contraindications the reader is referred to earlier articles (3, 5), but it should be mentioned here that the procedure is easily carried out under local anesthesia through a 1 cm. incision, and in properly selected cases is attended with very little risk. The advantages of peritoneoscopy over exploratory laparotomy are: (a) less risk and discomfort to the patient, (b) only one day's hospitalization, (c) local anesthesia and (d) stab incision. A biopsy may be obtained. Peritoneoscopy is contraindicated in serious cardiac or pulmonary disease and in intraabdominal or pelvic inflammation. Multiple adhesions constitute a relative contraindication. The indications for peritoneoscopy include obscure abdominal or pelvic disease to establish a positive diagnosis and to plan treatment. The procedure has proven of value in neoplasm, cirrhosis, tuberculous peritonitis,

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ascites, pelvic tumors, ectopic pregnancy, and ovarian dysfunction.

In our series of 100 peritoneoscopies, 61 cases have been directly related to the gastro-intestinal tract, including the liver, gall bladder and pancreas. In some of the remaining cases of ascites, tuberculous peritonitis, etc., gastro-intestinal symptoms have been prominent. To the gastro-enterologist peritoneoscopy is useful in:

I. MALIGNANT DISEASE	35
1. Stomach	
a. Carcinoma	28
b. Sarcoma	1
c. Lymphoma	1
2. Cecum, colon and rectum	
a. Carcinoma	5
II. LIVER DISEASE	20
a. Cirrhosis	9
b. Primary carcinoma	3
c. Miscellaneous	8
III. MISCELLANEOUS	45
a. Tuberculous peritonitis	6
b. Gynecological	24
c. Unclassified	15

100

I. MALIGNANT DISEASE

Probably the most frequent and important use is in malignant disease to determine operability and to save unnecessary exploratory operations. The prognosis and treatment of cancer anywhere in the body may be materially altered by finding the liver or peritoneum full of metastases. We will consider primary malignant disease of the gastro-intestinal tract first. In neoplasm of the esophagus, for example, if the liver shows carcinomatous infiltration, any hope of resection will be abandoned, gastrostomy may be avoided and the esophageal lumen maintained by passing bougies over a previously swallowed string as a guide (13).

1. STOMACH—CARCINOMA, SARCOMA, LYMPHOMA

Much more common of course is carcinoma of the stomach, and it is in this disease that we have used the peritoneoscope more than in any other condition. Since exploratory laparotomy for carcinoma of the stomach carries with it a very high mortality, the information obtained by peritoneoscopy regarding the presence or absence of metastases in the liver and peritoneum is of great importance in advising for or against operation. A relatively small non-obstructing carcinoma of the stomach, clinically presumed to be operable, may have already metastasized to the liver, making operation for cure impossible, and palliative resection unjustifiable. On the other hand, a large palpable gastric neoplasm clinically supposed to be inoperable, may be shown by peritoneoscopy to have left the liver and anterior peritoneal cavity uninvolved. Carcinoma of the stomach has been the preliminary diagnosis in 28 cases. In 12 of these the lesion was considered operable at the time of peritoneoscopy and this was later confirmed by resection. Three cases considered operable by peritoneoscopy were not resected for various reasons. [1 patient had probable involvement of the lower esophagus by X-ray and questionable perirectal glands; 1 patient died at the time of a preliminary jejunostomy, and the third patient was

not operated upon because of a complicating coronary thrombosis]. Eight cases, however, showing no involvement of the liver or anterior peritoneum by peritoneoscopy, were found to be inoperable due to posterior fixation, invasion of the pancreas, lesser peritoneal cavity, or other adjacent structures. With increasing experience in the technic of peritoneoscopy it has been possible to note adhesions between the stomach and the liver with or without the probability of direct extension of the growth. Serosal involvement along the greater curvature has also been noted and in one case a positive biopsy was obtained from a lymph gland along the greater curvature. Positive biopsies from carcinomatous implants in the liver have proven very satisfactory. But so far at least the question of posterior fixation can only be determined by open operation. The remaining 5 cases in this group were considered inoperable by peritoneoscopy. In 3 of these a positive biopsy was obtained—twice from the liver and once from a lymph gland along the greater curvature. In the latter case a chylous ascites was also present and although the patient was almost certainly inoperable, at the family's insistence he was explored, found to be inoperable, and the peritoneoscopic findings confirmed. In the other 2 cases tiny implants were seen in the liver and peritoneum but no biopsies were obtained and the patients were not explored. In summary then of the 28 cases in this group, the information obtained at peritoneoscopy was proved to be correct in 17 cases, was almost certainly correct in 3 cases, and in the remaining 8 cases the information given was essentially correct but was insufficient to forestall exploratory laparotomy owing to extension of the disease posteriorly, or otherwise beyond the reach of the peritoneoscope.

As an example of a large gastric neoplasm found to be operable, I will cite the following case:

Case 1. J. E. (M. G. H. U. No. 172079,) a 53 year old male, American laborer, entered the hospital on February 11, 1939, complaining of epigastric pain of 11 months' duration. The pain was unassociated with and unrelieved by eating. There had been a loss of weight of 23 lbs. in 8 months. There was moderate distention and belching but no nausea or vomiting. X-ray examination of the stomach showed a large filling defect involving the proximal 2/3 of the stomach. This portion of the stomach was firm and stiff and apparently contiguous with an epigastric mass which was easily palpated. The clinical impression was that of extensive gastric malignancy. Because of fever and upper respiratory infection, peritoneoscopy was postponed until 10 days after admission at which time it was reported as follows:

"Under local anesthesia an incision 1½ cm. long was made in the midline just below the umbilicus, the peritoneal cavity inflated with air, and the Ruddock peritoneoscope introduced. The liver showed no evidence of metastatic disease anywhere throughout either right or left lobe. The edge appeared sharp and normal. Linear striations were rather marked, and near the edge the anterior surface was slightly greyish. The peritoneoscope was introduced between the liver and the stomach, and showed no evidence of adhesions between the stomach and the liver as far as could be determined. No evidence of serosal involvement of the stomach was demonstrable. There was no free fluid. There was no evidence of metastatic disease in the omentum or peritoneal cavity. The intestines were well collapsed, presumably aided by the enema and pitressin. Conclusions: Negative peritoneoscopy. Advise surgical exploration."

Three days later the patient was operated upon and no metastases found anywhere in the liver, peritoneum or pelvis. Subtotal gastrectomy was performed. Unfortunately, bronchopneumonia and cerebral thrombosis developed postoperatively and the patient died. The pathological report from the resected specimen was polypoid adenocarcinoma—lymph nodes negative.

COMMENT

In this case we had a history of long duration, no obstruction, and a palpable mass with a clinical impression of "extensive gastric malignancy." Such a patient might well have been considered clinically inoperable, yet peritoneoscopy showed no metastases, and the growth was resected without difficulty.

In the following case peritoneoscopy was useful in establishing a positive diagnosis of inoperable gastric carcinoma.

Case 2. F. S. T. (Baker Memorial Hospital U. No. 127931), Male, 57, two years before entry noticed loss of appetite, indigestion and abdominal pain. Physical examination on admission revealed a palpable mass in the epigastrium and liver edge 4 cm. below costal margin, probably nodular. X-ray examination on two occasions, (5 12 38 and 5 14 38) was unsatisfactory due to retained secretion and food—"the nature of the obstructing lesion in the region of the pylorus cannot be definitely demonstrated but seems highly suggestive of ulcer." Gastroscopy performed on May 10, 1938, showed on the lesser curvature near the pylorus an ulceration about 5 x 3 cm. with ragged nodular proliferating margins and a dirty gray base. The gastroscopic diagnosis was carcinoma. At times the patient was slightly obstructed and operation was considered. The surgical consultant, however, advised against operation. Before refusing to give this patient the possible benefit of a resection or palliative operation, it was thought advisable to make certain by peritoneoscopy regarding the question of liver or peritoneal metastases. Accordingly, peritoneoscopy was performed on May 23, 1938, and showed the liver throughout to be "studded with yellowish nodules varying in size from 3 or 4 mm. to 2 or 3 cm. in diameter, and having the characteristic appearance of carcinoma. The anterior serosal wall of the stomach appeared normal, there being no evidence of neoplasm. There was no evidence of metastatic disease in the peritoneum of the upper abdomen and none could be seen in the omentum so far as was examined. An anterior gastro-enterostomy would appear to be possible. A biopsy was taken from one of the larger lesions on the anterior surface of the liver. There was very little bleeding." Before the biopsy report was obtained, X-ray treatment was given on the basis that the lesion might be lymphoma. There was a rather remarkable clinical improvement for a short time. The biopsy, however, was reported metastatic carcinoma.

COMMENT

Although the clinical impression in this case was that of inoperable carcinoma of the stomach, peritoneoscopy with biopsy established a positive diagnosis of metastatic carcinoma of the liver. This was particularly important in this case in view of the good response to X-ray therapy which raised the question of lymphoma as a diagnosis. The importance of gastroscopy (14, 15) in this case should also be emphasized.

In the following case of sarcoma of the stomach, peritoneoscopy gave important information.

Case 3. H. G. F. (Baker Memorial Hospital U. No. 31604), Male, 46.

1 14 35. Partial gastrectomy for sarcoma of the stomach.

1/31/38. The patient reentered because of a large mass apparently connected with the liver noted four months ago. X-rays taken then showed displacement of the stomach to the left by this mass. A prolonged course of X-ray therapy was followed by relief of symptoms and the mass at time of entry appeared to be questionably smaller, freely movable and probably not connected with the liver. Peritoneoscopy showed the liver and liver edge apparently free of malignant disease and probably separate from the tumor mass. There was no evidence of metastatic disease throughout the peritoneum. A week later palliative resection of the recurrent (spindle cell) sarcoma was performed.

COMMENT

Peritoneoscopy in this case demonstrated that a recurrent sarcomatous mass did not involve the liver and was probably resectable. Laparotomy confirmed these observations, and the recurrent mass was removed.

Gastric lymphoma was the probable diagnosis in the following case:

Case 4. W. K. (M. G. H. U. No. 86095), Male, 66, entered the hospital on October 30, 1937, complaining of anorexia, swelling of abdomen and progressive weakness of three months' duration. Physical examination—marked ascites. X-ray examination of the stomach showed a diffuse process involving the upper two-thirds, probably infiltrating type of tumor. A very marked inflammatory swelling of the mucosa could not be definitely excluded, but was felt to be much less likely.

Gastroscopy did not suggest carcinoma but favored an inflammatory process or lymphoma. Peritoneoscopy was reported as follows: "Under local anesthesia an incision about 2 cm. long was made in the midline just below the umbilicus. Abdomen inflated with air and Ruddock peritoneoscope introduced in the usual manner. The liver appeared entirely normal. Surface smooth, edge sharp, color brown. The gall bladder appeared a deep purplish-blue and very vascular. The upper part of the stomach could not be seen as the liver was overlying it. Along the lesser curvature there was marked engorgement of the vessels, but the serosa appeared normal. The anterior wall of the stomach appeared normal. The omental vessels throughout were markedly engorged. Loops of bowel appeared normal. Peritoneal surface of anterior abdominal wall appeared normal, diaphragm normal. There was no evidence of metastatic malignancy anywhere in the liver or peritoneum. There was a considerable amount of slightly cloudy, grayish fluid in the dependent portion, 530 cc. of which was removed. The incision was left open to facilitate drainage of the ascitic fluid. The findings can probably be all explained on the basis of lymphoma. A general abdominal carcinomatosis and cirrhosis of the liver have been ruled out." Definite improvement followed X-ray treatment. Repeated paracentesis was necessary, the last one before death (5/20/38) yielding six quarts of white cloudy fluid.

COMMENT

This case essentially was one of unexplained chylous ascites, in which peritoneoscopy excluded carcinomatosis and cirrhosis and made the diagnosis of lymphoma most probable.

b. CARCINOMA OF CECUM, COLON AND RECTUM

In carcinoma of the large bowel peritoneoscopy is less frequently indicated because colostomy for relief of obstruction is so often imperative, and at the time of colostomy the abdomen can be explored. We have, however, performed peritoneoscopy in one case of carcinoma of the cecum, one case of carcinoma of the

colon and three cases of carcinoma of the rectum. In the patient with carcinoma of the cecum the liver was found to contain metastatic carcinoma (positive biopsy obtained) and there was a small amount of free fluid in the abdomen. In view of these findings and the absence of obstruction laparotomy was not advised. On the theory that this patient would later become obstructed, laparotomy with ileotransverse colostomy was, however, performed and confirmed the peritoneoscopic findings. In the case of carcinoma of the colon an adenocarcinoma of the descending colon had been resected six months earlier, symptoms of subacute obstruction had appeared but the patient was able to tolerate a liquid diet. Peritoneoscopy showed carcinoma had invaded the liver and a positive biopsy was obtained. No other operation was performed. Two months later this patient died and autopsy confirmed the peritoneoscopic findings. A brief resumé of the three rectal cases follows:

Case 5. M. E. C. (M. G. H. U. No. 55769), Female, 69. Peritoneoscopy showed no involvement of the liver. A mass in the right lower quadrant was seen to be covered by fatty omentum and thought to be inflammatory. Colostomy was done later, however, and the mass was shown to be malignant.

Case 6. A. C. (M. G. H. U. No. 79155), Female, 40. Peritoneoscopy showed "liver surface to be granular throughout but no nodules suggestive of carcinoma were seen on the surface. On the right anterolateral border of the right lobe, however, there appeared to be a slight swelling which could represent metastatic disease inside the liver." As the patient was showing obstructive symptoms a colostomy was done, at which time palpation of the liver revealed metastases.

Case 7. W. L. (M. G. H. U. No. 18665), Male, 65. 2/10/37. Colostomy and posterior excision of the rectum for carcinoma.

9/3/38. Patient reentered with a story of 2½ weeks of painless jaundice. The presumptive diagnosis was metastatic carcinoma of liver. Peritoneoscopy was indicated to either confirm this diagnosis and show the extent of the disease or to demonstrate absence of metastatic disease. Peritoneoscopy was done on September 9, 1938, and showed no evidence of metastatic disease in the liver or anywhere in the peritoneum. The gall bladder could not be seen. Operation was undertaken on September 20, 1938, the gall bladder was found to be small and contained several stones. There was one large stone which protruded through the dilated cystic duct into the common duct. On removing this there was a free flow of bile. No evidence of metastatic malignancy was found. At a later operation, October 26, 1938, the common duct was explored and a common duct stone crushed. Following these operations the patient made an uneventful convalescence and was doing well three months later.

SUMMARY

In summary of these five cases of carcinoma of the large bowel, it may be said that peritoneoscopy was of no value in two cases (rectal cases 5 and 6). In the case of carcinoma of the cecum with metastases to the liver there was little to be gained by peritoneoscopy since ileotransverse colostomy was performed anyway. It is debatable, however, whether with dietary measures ileotransverse colostomy might not have been avoided under such terminal conditions. In the case of carcinoma of the descending colon peritoneoscopy established a positive diagnosis of metastatic disease in the liver. In the final case of carcinoma of the rectum peritoneoscopy gave definitely helpful

information by showing the liver and peritoneum to be free of metastatic disease.

II. LIVER DISEASE

a. Cirrhosis

Peritoneoscopy has been performed here in nine cases involving a differential diagnosis of cirrhosis of the liver, neoplasm, lymphoblastoma, tuberculous peritonitis and unexplained ascites. In seven of these the peritoneoscopic finding of a coarsely granular or hobnailed liver was considered sufficient evidence to make a positive diagnosis of cirrhosis. Ascitic fluid was present in two of these. Biopsy was unsuccessful in one, showing only fibrosis, probably from a very thick liver capsule. In the eighth case the differential diagnosis lay between cirrhosis of the liver and neoplasm; peritoneoscopy here revealed a hobnailed appearance and a positive biopsy showing cirrhosis was obtained. In the ninth case the same differential diagnosis arose between cirrhosis and neoplasm, but peritoneoscopy revealed a normal liver and although subsequent laparotomy with choledochostomy was reported as showing biliary cirrhosis, the pathological report of a biopsy from the liver showed only slight obstructive cirrhosis.

The following case reports suggest the value of peritoneoscopy in the differential diagnosis of cirrhosis of the liver and malignant disease.

Case 8. B. F. N. (Baker Memorial Hospital U. No. 87002), Male, 71, entered the hospital November 3, 1938, complaining of anorexia, constipation, gaseous indigestion and cramp-like pain of two months' duration. One week before admission he became distended, obstipated and nauseated at the sight of food. Physical examination showed a tremendously distended abdomen with shifting dullness in both flanks. Paracentesis yielded three quarts of milky fluid after which the liver edge could easily be felt 5 cm. below the costal margin. A mass was also palpable in the epigastrium which was thought to be either the left lobe of the liver or gastric tumor. Two months prior to admission, X-ray examination of the stomach showed a large ulcerating lesion on the lesser curvature with a filling defect in this region. Malignancy could not be excluded. Gastroscopic examination at that time was unsatisfactory, but, as far as could be determined, there was no evidence of carcinoma. Neither X-ray nor gastroscopic examinations were wholly satisfactory because of the patient's very large size.

Another complicating factor in this case was a mild diabetes mellitus with a blood sugar of 143 mgm. %. This was controlled by protamine insulin units 20 daily. Operation for possible malignancy of the stomach was out of the question. Peritoneoscopy performed on November 8, 1938, showed the liver to be small with nodular, granular markings, suggestive of cirrhosis. 14 oz. of chylous fluid was removed. There was no evidence of malignant disease. After general medical care, he was discharged home on November 26, with a diagnosis of cirrhosis of the liver, diabetes, and question of cancer of the stomach. Five days later his local physician reported that he died at home of hemorrhage.

COMMENT

In this patient peritoneoscopy definitely established a diagnosis of cirrhosis of the liver and showed no evidence of metastatic carcinoma.

In the following case the differential diagnosis also lay between cirrhosis of the liver and malignant disease.

Case 9. L. N. (Baker Memorial Hospital U. No. 173770), Male, 53, entered the hospital on January 23, 1939, com-

plaining of swelling of the abdomen and obesity. He had always been over-weight and his intake of food and alcohol had been excessive for many years. Three years before entry he was put on a reducing diet and his weight came down to 200 lbs. Three months before entry his abdomen was swollen. He noted edema of the legs and orthopnea, requiring three pillows. There had been no jaundice. The clinical impression was alcoholic cirrhosis of the liver. The question of cancer superimposed on cirrhosis was raised and peritoneoscopy was therefore performed on January 27. Two and one-half pints of slightly reddish-brown fluid were aspirated. The peritoneal cavity appeared normal throughout except for an excessive amount of fat in the omentum and mesentery and an abnormal liver. The liver was definitely hobnailed throughout. Two satisfactory biopsies were taken from the anterior surface of the left lobe and the wound coagulated with diathermy. The pathological report was cirrhosis of the liver.

COMMENT

Peritoneoscopy in this case was helpful in establishing a positive diagnosis of cirrhosis of the liver by biopsy. A superimposed carcinoma was excluded.

Case 10. B. P. S. (Baker Memorial Hospital U. No. 128598), Male, 69, entered the hospital on May 16, 1933, complaining of abdominal cramps and diarrhea of two months' duration. Anorexia had been noted for six months. There had been 13 lbs. weight loss and progressive weakness during the past two months. Past history—syphilis treated four years ago with further antiluetic therapy seven years ago. Arteriosclerotic heart disease with mural fibrillation of twelve years' duration controlled by digitalis—bronchopneumonia four years ago. Physical examination showed an enlarged heart, irregular heart sounds of fair quality but distant and soft blowing systolic murmur over the precordium, heard loudest at the apex. Abdomen showed definite tenderness with a suggestion of a mass in the region of the cecum. The liver edge was palpable about 2 cm. below the costal margin and was questionably nodular. Laboratory findings: Hinton—positive; Wasserman—strongly positive; van den Bergh—too low to read. Gastro-intestinal X-ray: The esophagus, stomach and duodenum showed no definite evidence of intrinsic disease. The usual pressure defect of the spine across the stomach appeared to be considerably larger than usual, suggesting an epigastric mass in the region of the body of the pancreas or left lobe of the liver. X-ray diagnosis: Question of carcinoma of the body of the pancreas. Peritoneoscopy, May 20, 1933. The liver appeared markedly granular throughout with some areas presenting a round hillocky appearance. The edge of the liver was rounded—both the right and left lobes were seen on the anterior and superior surfaces up to the diaphragm. There was no evidence of metastatic tumor anywhere in the liver. The patient was discharged on May 24 with a diagnosis of cirrhosis of the liver. Malignancy was still suspected but could not be found. The subsequent course of this patient has indicated that we are apparently not dealing with malignant disease, for although he has not done well, he is still up and about and no malignancy has been demonstrable during the past year.

COMMENT

Peritoneoscopy in this case was helpful in making a diagnosis of cirrhosis of the liver and excluding so far as possible a diagnosis of carcinoma.

Regarding peritoneoscopy in cirrhosis of the liver it may therefore be said that although the diagnosis of cirrhosis is often made clinically with reasonable certainty there are cases where the diagnosis is doubtful or well-nigh impossible. It is in such cases that peritoneoscopy has been of definite value in establishing a positive diagnosis.

b. LIVER—PRIMARY CARCINOMA

Three cases in this series have fallen into this group because clinically the question of primary carcinoma of the liver was seriously considered. In the first case the clinical diagnosis lay between liver abscess and malignancy. Peritoneoscopy showed a large liver but no abscess or neoplasm was demonstrable. At subsequent laparotomy, after much dissection there was demonstrated a bulging of the under surface of the liver which was thought to be due to abscess. This area was marsupialized and at a secondary operation was shown to be carcinomatous, probably primary. No wonder this could not be demonstrated by peritoneoscopy! In the second case peritoneoscopy disproved a clinical diagnosis of primary carcinoma of the liver, showing only hypertrophy of an otherwise apparently normal liver. This was subsequently confirmed by exploratory laparotomy, which revealed a normal liver and a retroperitoneal cortical cell adenoma of the adrenal. In the third case a clinical diagnosis of primary carcinoma of the liver was made. At peritoneoscopy "the liver throughout was studded with yellow nodular masses varying in size from $\frac{1}{2}$ to 3 or 4 cm. in diameter, many of them coalescing and having the typical appearance of carcinoma. From the peritoneoscopic appearance, it is like most of the metastatic carcinoma which I have seen, but as no primary source has been found it may be primary carcinoma of the liver. A large satisfactory biopsy was taken from the anterior surface of the left lobe." The biopsy report was adenocarcinoma.

In these three cases therefore peritoneoscopy was of no help in the first (a difficult case to diagnose even at exploration), gave correct and helpful information in the second, and gave a positive diagnosis (with biopsy) in the third.

c. LIVER—MISCELLANEOUS

In this group eight cases are listed as follows:

Case 11. J. DeC. (M. G. H. U. No. 129901), Male, 44. Clinically a right upper quadrant mass was palpable, but no positive diagnosis was possible. At peritoneoscopy "the anterior surface of both lobes of the liver appeared entirely normal and the liver edge appeared normal, except from the right lobe there was projecting a bluish-gray cystic appearing mass about the size of a lemon, covered superficially with several blood vessels and very smooth and glistening. This mass was continuous with the edge of the liver. On the lower part of it was a pearly-gray slightly elevated nodule about 2 cm. in diameter, which could represent neoplasm, but which may be simply a fibrous thickening of the wall. The whole mass could be a very much distended gall bladder, though it is somewhat to the right of the usual location. It could also be cystic disease of the liver. It extends about 8 to 10 cm. below the costal margin. The stomach and intestinal tract and peritoneum appeared normal.

Conclusions: The mass is probably cystic, ? of distended gall bladder, ? of cyst of liver. Suggest Graham test and ? of exploration. This patient was later operated upon, and the mass proved to be a cystic gall bladder, which was removed.

Case 12. L. M. D. (Baker Memorial Hospital U. No. 88897), Female, 60. This patient had had one eye enucleated for melanotic sarcoma and entered the hospital with a large liver. The clinical diagnosis was metastatic melanotic sarcoma of the liver. This was confirmed by peritoneoscopy (positive biopsy).

Case 13. M. H. (M. H. G. U. No. 350948), Female, 60. A diagnosis of polycystic liver and kidneys had been made

by operation at a previous admission several years previously. The diagnosis of polycystic liver at this admission was confirmed by peritoneoscopy.

Case 14. C. J. (M. G. H. U. No. 159996), Male, 59. In this case the differential diagnosis was between malignant disease and catarrhal jaundice. Peritoneoscopy showed no evidence of malignant disease in the liver, gall bladder, or peritoneum.

Case 15. M. E. K. (Baker Memorial Hospital U. No. 181460), Female, 35. This patient had had her breast removed for carcinoma several years prior to admission. On entry she showed an enlarged liver with ascites. The presumptive clinical diagnosis was metastatic carcinoma of the liver, but cirrhosis was also considered possible. Peritoneoscopy revealed a liver which looked cirrhotic, but the biopsy was reported as carcinoma. She ran a rapidly downhill course and died within a month.

Case 16. N. McI. (M. G. H. U. No. 330594), Male, 60. In this deeply jaundiced patient a clinical diagnosis of carcinoma of the gall bladder was suggested. Peritoneoscopy showed the liver to be studded with elevated nodules, having the appearance of carcinoma. Autopsy confirmed this diagnosis and showed the primary source to have been bronchogenic carcinoma (clinically wholly unsuspected!). This case is of particular interest as it was the first one ever performed at the Massachusetts General Hospital (January 10, 1936) and was done with a thorascop.

Case 17. L. S. (M. G. H. U. No. 353058), Male, 66. In this Italian-born patient the question of echinococcus cyst was raised, but peritoneoscopy revealed a normal liver.

Case 18. I. K. (Baker Memorial Hospital U. No. 43671), Male, 62. This patient's sole complaint was anorexia of one month's duration, and slight soreness in the left upper quadrant. Physical examination showed a large smooth upper abdominal mass, larger on the left. X-ray study: Gastro-intestinal series negative, barium enema negative. Chest plate revealed a circumscribed circular mass 5 cm. in diameter at the apex of the left lower lobe consistent with a solitary metastasis from a hypernephroma or with primary bronchogenic carcinoma. In view of the complete absence of pulmonary symptoms and an X-ray which suggested enlargement of the left kidney, cystoscopy and pyelogram were done which revealed no evidence of renal pathology. At peritoneoscopy the liver was found studded with umbilicated nodules, biopsy of one of which was reported adenocarcinoma.

In this group peritoneoscopy gave correct information in all eight cases, sometimes confirming a probable diagnosis, sometimes helping toward a correct diagnosis by exclusion, and at other times (as in Case 11) leading directly to the final diagnosis.

III. MISCELLANEOUS

It is difficult to group peritoneoscopy cases according to any set classification. Since this report is concerned primarily with gastro-intestinal disease, an attempt has been made to conform to a classification related to gastro-enterology. There are, however, many patients presenting gastro-intestinal symptoms who have no primary disease of the gastro-intestinal tract. For this reason it is important for the gastro-enterologist to recognize the value of peritoneoscopy in such cases as tuberculous peritonitis and pelvic tumors.

a. TUBERCULOUS PERITONITIS

The six cases in this group are of particular interest to the gastro-enterologist for all of them presented some gastro-intestinal symptoms including abdominal pain, anorexia, nausea, vomiting, sour eructations,

diarrhea and loss of weight. In two cases where the clinical impression was tuberculous peritonitis peritoneoscopy showed no evidence of it. Further study in one of these revealed a probable regional ileitis by X-ray, but in the other case the clinicians clung to a diagnosis of mesenteric gland tuberculosis, which could not be excluded by peritoneoscopy. A brief summary of the other four cases follows:

Case 19. D. D. (M. G. H. U. No. 352111), Female, 30.

History: Four months of slight progressive increase in size of abdomen. Recent abdominal pain, diarrhea, nausea and vomiting.

Physical examination showed a distended abdomen with shifting dullness.

Clinical impression was tuberculous peritonitis, but the question of cirrhosis of the liver was raised.

Peritoneoscopy showed the anterior abdominal wall, large and small bowel, round ligament of the liver, broad ligament of the uterus everywhere studded with fine tubercles. One gallon, 22 oz. of straw-colored fluid was removed and replaced with air.

Final diagnosis: Tuberculous peritonitis. Pulmonary tuberculosis.

Case 20. G. H. (M. G. H. U. No. 88618), Male, 23.

History: Three months swelling of abdomen, loss of weight, sour eructations, lassitude and night sweats.

Physical examination showed a full abdomen looking ascitic but without positive physical evidence; slight splenomegaly.

Clinical impression: ? tuberculous peritonitis, ? lymphoma.

Peritoneoscopy: Abdomen completely filled with filmy adhesions some of which showed multiple pinpoint whitish-yellow tubercles on them.

Final diagnosis: Tuberculous peritonitis. Inactive pulmonary tuberculosis.

Case 21. R. S. T. (M. G. H. U. No. 178952), Male, 41.

History: Two years of pain in the left flank, weakness, loss of weight and diarrhea.

Physical examination: Essentially negative.

Clinical impression: ? carcinoma of sigmoid, lymphoma, diverticulitis, tuberculosis, lymphogranuloma inguinale.

Peritoneoscopy showed multiple punctate lesions 1-2 mm. in diameter on the surface of various loops of small bowel. These were consistent with tuberculous peritonitis.

Final diagnosis: Tuberculous peritonitis; pulmonary tuberculosis; ? tuberculosis of cecum.

Case 22. B. P. (M. G. H. U. No. 166987), Female, 18.

History: Three months generalized abdominal pain with chills, fever, vomiting, diarrhea, and swelling of abdomen.

Physical examination showed shifting dullness and a fluid wave.

Clinical impression: Tuberculous peritonitis.

Peritoneoscopy: Numerous fine translucent elevations typical of tuberculous peritonitis. Biopsy showed tuberculosis.

In summary of these six cases peritoneoscopy excluded a diagnosis of generalized tuberculous peritonitis in two, and confirmed or established with certainty a diagnosis of tuberculous peritonitis in four, with positive biopsy in one. In one case air was purposely left in the peritoneal cavity, hoping it would be beneficial in treatment.

b. GYNECOLOGICAL

Many cases that eventually turn out to be gynecological may present gastro-intestinal symptoms. In a discussion of this sort, therefore, such a possibility must not be overlooked and the value of peritoneoscopy in differential diagnosis should be mentioned. We have

done peritoneoscopy in twenty-one cases involving a diagnosis of pelvic tumor or ovarian dysfunction. A general review of these is beyond the scope of this paper, but the following case will serve as an example:

Case 23. M. E. B. (M. G. H. U. No. 355031), Female, 65.

History: Four months increase in size of abdomen with vomiting, constipation and loss of weight. Two months ago noted a hard painless lump in right abdomen.

Physical examination showed a distended abdomen with fluid wave and a large firm fixed mass which appeared to fill the whole lower abdomen. By rectum nodules were felt in the pouch of Douglas.

Clinical impression: Carcinomatosis arising from the ovaries.

Paracentesis—2 quarts of greenish-yellow fluid. No tumor cells seen on pathological examination.

Peritoneoscopy: The entire lower abdomen was occupied by a large, smooth, pearly-gray mass from which a biopsy was obtained. The anterior peritoneum appeared to contain metastatic nodules.

Pathological report: Metastatic carcinoma.

Treatment: X-ray therapy.

Final diagnosis: Ovarian carcinomatosis.

DISCUSSION

Peritoneoscopy has been done on 100 patients. One fatality, previously reported (5), occurring in the 11th case done, was due to an error in judgment in subjecting a patient in the terminal stages of multiple lung abscess, coronary disease and possible echinococcus cyst of the liver, to the stress and strain of sedative drugs and peritoneoscopy. Subcutaneous emphysema was produced in a few of the earlier cases, but otherwise there have been no complications. The procedure is therefore safe in properly selected cases. In order to acquire judgment in its use and skill in manipulation of the instrument peritoneoscopy should be concentrated in the hands of a few physicians or surgeons. One would think from a surgeon's knowledge of abdominal and pelvic pathology, and operative technic, that the procedure should be done by one trained in surgery. Ruddock, however, is a physician. He has been responsible for the recent revival of interest in this method and has had notable success with it. The procedure requires much patience and forbearance, and there are occasions when the operator will be exasperated at being so near an organ and yet unable to see it as well as he would like to, or to grasp it in his hand. Some surgeons, therefore, would probably be temperamentally unsuited to using the peritoneoscope. In general, however, some training in abdominal and pelvic surgery is most desirable.

From a review of the cases presented above one cannot escape the conclusion that peritoneoscopy is a valuable procedure. It will replace exploratory laparotomy in certain cases, but its limitations must be recognized. It is difficult and often impossible to see the posterior peritoneum or deep in the pelvis. On the other hand, the liver and anterior peritoneum are beautifully visualized. The pelvic organs are often very well seen, but the ovaries may lie posteriorly and be difficult or impossible to examine. The results have been most striking in malignant disease. Carcinoma of the stomach, without obstruction and of questionable operability, offers a definite indication for peritoneoscopy. In this regard Thieme (9) believes "it should be used routinely in carcinoma of the stomach to avert operation in the inoperable cases." In carci-

noma of the colon and rectum peritoneoscopy is less frequently indicated because colostomy may be urgent. When, however, there is no obstruction peritoneoscopy is indicated to determine liver or peritoneal metastases and to delay or avert colostomy if the disease is incurable. In diseases of the liver peritoneoscopy has been useful in confirming or establishing a diagnosis of cirrhosis, in differentiating cirrhosis from primary or secondary malignancy, in the study of unexplained jaundice, ascites, polycystic liver and echinococcus cyst. Of interest also to the gastro-enterologist is its use in tuberculous peritonitis where the peritoneoscopic findings are highly accurate. Its usefulness in pelvic pathology is also unquestionable, and here again such cases may present many gastro-intestinal symptoms, baffling sometimes even to the well trained internist. Though its limitations must always be borne in mind, peritoneoscopy will not infrequently lead to a positive diagnosis.

CONCLUSIONS

Peritoneoscopy is a safe, simple, and highly reliable diagnostic method. Errors in diagnosis have been very rare.

Peritoneoscopy will confirm or refute various doubtful clinical diagnoses. Positive diagnosis by biopsy is often possible.

Peritoneoscopy will avert exploratory laparotomy in certain cases.

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DISCUSSION

DR. JOHN L. KANTOR (New York City): This method, I think, has a future. It is a safe method, and in the few cases we have followed, patients can go about their business the next day, eat their meals the same night.

Differential diagnoses may be made, not so much in straight gastro-enterological cases, as in borderline cases. The diagnosis of cirrhosis in the preneoplastic stage is now one of the possibilities by this method.

Biopsies are being taken and give much information. Biopsy is usually taken from the liver or from metastatic implants on the parietal layer of the peritoneum. It is not so safe to take the specimen from the hollow viscera themselves. The biopsy is a little painful but not terribly distressing.

As far as the organization of this type of procedure is concerned, in my own hospitals we are trying to get a sort of team control and are grouping together all the endo-

scopic procedures—i.e. gastroscopy, peritoneoscopy, as well as proctoscopy—because we think they have a combined future.

DR. J. RUSSELL VERBRYCKE (Washington, D. C.): I congratulate Dr. Benedict on his mastery of this new procedure.

I think I had the first instrument released by Ruddock, and I am still trying to perfect myself in its technique. Every form of endoscopy, of course, has three steps: (1) the introduction of the instrument; (2) the visualization; and (3) the interpretation. The first is easy, the introduction, but certainly with peritoneoscopy in my hands, the visualization is not quite so easy; but, most of all, I have had difficulty with the interpretation. Things look so very different inside of the abdomen.

As I do more of this, I have mixed feelings, first a feeling of enthusiasm as to the wonderful possibilities of the method, and then one of intense humility with myself that I can't interpret better what I do see.

I have not yet reached the point where I am willing to put my work up with an absolute hundred per cent "yes" or "no."

I have brought just two slides I should like to show.

(Slide) These are some things I have been able to see; the upper left-hand corner, carcinoma of the liver, metastases, and one thing to be emphasized is that a good landmark to start from is shown here, the round ligament of the liver, which always shows very plainly. The second one was a very interesting case of definite cirrhosis throughout the liver, but there were those two larger nodules which several of us have interpreted as being most suspicious of carcinoma. We did not get a biopsy in this case because the electrocoagulation machine was not available at the time and it is dangerous without that.

The next demonstrates the way adhesions show as a sort of stalactite-stalagmite appearance and, of course, they are easy to determine and then the last picture shows what I take to be the easiest part of the abdominal cavity to see, the pelvis, when it is not complicated by too many adhesions.

(Slide) This is a variation of the one shown by Dr. Benedict. I have put in a couple more advantages than he and Dr. Ruddock have mentioned, and one disadvantage.

With an exploratory we have a limited view and no ordinary incision gives complete visualization of the abdomen, whereas we have a wide view of the entire abdomen through the peritoneoscope.

On the other hand with an exploratory we have the benefit of deep palpation which in peritoneoscopy the deep structures are not seen satisfactorily unless they push up through the mass of omentum and cores of bowel.

DR. RUDOLF SCHINDLER (Chicago): I also want to congratulate Dr. Benedict for giving us this excellent paper. I have two questions I want to ask.

I tried peritoneoscopy in 1922 and I gave it up for two reasons, the first not very important. My patients experienced quite some discomfort through the pneumoperitoneum, sometimes so disagreeable that I thought it was too much for a simple diagnostic procedure. I wonder how you avoid this type of discomfort.

The second question seems to me more important. I knew at that time, as a pathologist, that there often are diffuse adhesions of the peritoneal cavity and I knew from my experience with the cadaver, that I could not avoid with certainty puncturing the small intestines in such cases. Now I realize that it is not at all dangerous to get a puncture or a fistula of the intestine, but it is very disagreeable. I wonder how one can diagnose such diffuse adhesions before going in with the needle, and how to avoid such a fistula.

DR. EDWARD B. BENEDICT (Boston): In answer to Dr. Schindler, I must say that with thorough sedation we have had very little discomfort from the pneumoperitoneum. If there have been previous laparotomies, I am always careful to go through in another locality in the abdomen, and have had relatively little trouble from adhesions and no perforation of the bowel.

Now I should like to show the picture.

... Showing of motion picture "The Technique of Peritoneoscopy." ...

A Discussion of the Procedures Which Are Helpful in Diagnosing Lesions of the Esophagus

By

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OBVIOUSLY the progress of any science is dependent not only upon the ingenuity of its practitioners, but also inevitably upon developments in other fields. This has been, and still is the rule in the medical sciences. The fervid desire for truth and exactness prompted our early medical practitioners first to inspect and palpate the various organs of the patient, to percuss and finally to listen to certain vital processes.

Orificial examinations, however, were limited to palpation until there was sufficient development in the electrical world to permit of the development of endoscopy, and this, together with the discovery of X-rays has added more to our knowledge of the dis-

eases of such an inaccessible organ as the human esophagus, than have any other contributions.

Endoscopes developed for the purpose of esophagoscopy have, to the best of my knowledge, been rigid metal tubes of varying lengths. Some are telescopic and consist of two rigid barrels, one sliding through the other, and fitted with proximal lights. Others are single rigid tubes and derive their lighting facilities from a long light carrier fitted with the tiny "wheat seed" bulbs. One of the earlier types of single-tube instruments was provided with an obturator and designed to be passed through laryngeal speculum. The later forms of this instrument are made with the so-called slanting or "whistle tip" and are designed to be passed under direct vision without the aid of speculum or obturator. A suction tube is an integral part of the one-piece instruments while the telescopic types

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use a separate suction tube inserted as needed through the lumen of the instrument itself.

It is not my purpose to discuss the virtues of the various instruments. Whichever instrument one uses best is the one for him to use. I, personally, was taught to do esophagoscopy with a single piece instrument using an obturator. The patient was seated on a low stool and the instrument passed through a laryngoscope. With a well trained assistant to hold the head, this worked very well and good control over the patient was obtained. Currently, Dr. E. B. Freeman and myself use the instrument with the "whistle tip" introduced under direct vision with the patient in the supine position. This, I feel sure, affords the patient more comfort but is no safer or more sure of introduction than the obturator instrument. An instrument with adequate facilities for removal of secretions, sufficient caliber for good vision and use of biopsy forceps, and of sufficient length to reach the lesion, is a good instrument to use.

The discovery of non-toxic opaque materials suitable for introduction into the stomach paved the way for a very useful diagnostic method following the discovery of the X-rays. Used in liquid or semisolid mixtures, these materials furnish a ready means for both screening and filming of the esophagus. A "00" gelatine capsule lightly filled with barium also furnishes a useful device for determining the degree of obstruction and particularly in malignant strictures in gauging the induration and consequent rigidity of the esophageal wall. When swallowed with plain water, this device, if lightly filled, floats on the surface and comes to rest at the stricture or passes on through, depending upon the degree of obstruction and amount of rigidity. Of such a device, Ross Goldin states in Nelson's System of Radiology that a small foreign body, such as a small bone, imbedded in the esophageal wall, on contact with the capsule will cause it to be tumbled over and over, thereby indicating the position of the foreign body.

Grasping forceps for the removal of foreign bodies, devices for closing open safety pins and biting forceps equipped with jaws and a grating for the removal of adequate biopsy material have, as we know, reached a high standard of perfection.

The problem of evaluating the factors contributing to a correct diagnosis of esophageal diseases is rather difficult, if one is to compare them one with the other. However, considered in the light of their respective uses, it is rather easy to see the importance of each diagnostic factor.

In the beginning, for example, a comprehensive history is essential. The foremost symptom of esophageal disease is dysphagia. In a discussion of the symptoms of esophageal diseases in general, Dr. Freeman states that "dysphagia, pain and regurgitation of esophageal contents are the most prominent symptoms."

Beyond these symptoms, lie an array of other symptoms by means of which we endeavor to differentiate the numerous diseases affecting the esophagus. It seems to be generally accepted among authorities, that if more difficulty is experienced in the swallowing of solid food, the condition is apt to be due to a eareinomatous stricture. Conversely, if more difficulty is caused by liquids than by solids, one is apt to be dealing with a so-called cardiospasm or achalasia. Kantor states that substernal or precordial pain, radiating

through to the back, precedes dysphagia in most cases of peptic ulcer of the esophagus, and regurgitation, pain and hemorrhage may follow. Verbrycke reported twenty-three cases of chronic cardiospasm in which the pain simulated angina pectoris. Von Pannewitz (Freeburg) Roentgen Praxis, July, 1937, reported a case of primary traction and secondary pulsion diverticulum of the anterior portion middle third of the esophagus in which the symptoms were precordial pain radiating to the left upper abdomen. Vinson remarked before the X-ray Section of the Eastern Seaboard in Washington, February, 1939, that rather large benign tumors of the esophagus usually caused no apparent esophageal obstruction because of the remarkable adaptability of the remaining normal esophageal wall. Thus, one finds in the literature a variety of unusual symptoms found in various esophageal conditions. It seems apparent therefore that the history and symptoms are indispensable as a means of determining that esophageal disease exists, the actual nature of which must be sought by other means at our disposal.

In this day, every gastro-enterologist is quite familiar with the usual radiological appearances seen in the obstructed or partially obstructed esophagus, and almost all practitioners are well aware of the usefulness of X-rays as an aid in esophageal diagnosis, even though they are not intimately conversant with the differential details manifest in the various lesions. It is apparent, therefore, that anyone complaining of symptoms distinctly referable to the esophagus, finds his way very promptly into the hands of someone capable of making an intelligent radiologic examination. The reason for this becomes more evident when one stops to consider the character of this type of examination. The foremost consideration which recommends a radiologic examination is its ready availability and universally accepted utility. Nonetheless important, however, is the fact that such an examination, while amazingly accurate, is quite easy to make and not usually painful or unpleasant to the patient himself. This latter fact makes this examination indispensable as a diagnostic aid. Spasms, strictures, diverticula and dilatations are readily recognizable by a thorough screening, using a suitable opaque meal and oftentimes benign and malignant lesions can be safely differentiated and the presence of a gastric lesion impinging on the lower esophagus detected.

There remain, however, certain details of a thorough investigation, undetectable by any other means than a careful endoscopic study, most particularly since, in a certain number of instances, the obtaining of biopsy material is indispensable. In such instances, esophagoscopy examinations cannot be avoided. Here, both patient and physician are faced with a procedure which while extremely necessary, is neither as comfortable nor as universally available as the radiographic examination. Such services are obtainable, however, in most of the larger cities and are relatively innocuous in the hands of a competent endoscopist.

It is not my purpose to enter into a controversy as to which speciality esophagoscopy belongs. Adroitness in the use of the esophagoscope is essential to a successful examination but is not the sole requisite of a competent esophagoscopist. One who has reasonable

skill in the passage of the instrument and can recognize gross pathology with reasonable accuracy—checking constantly with the microscopic findings—is a competent esophageal diagnostician. One who is an incompetent gastroscopist may be able to pass the instrument but an incompetent endoscopist will seldom be able to pass an esophagoscope beyond the inferior constrictor of the pharynx. Esophagoscopy is one of the most difficult endoscopic procedures in use. If it seems necessary to use force to pass the inferior constrictor muscles the examination had best be postponed until the patient is better relaxed and in a more cooperative mood. Yet, in the hands of a competent well-trained person, esophagoscopy is a perfectly safe procedure and a general anaesthetic is seldom necessary for a successful examination. Local application of a 10% cocaine solution following morphia Grs. $\frac{1}{4}$ and atropine Gr. 1 100 administered hypodermatically, one hour previous to the examination, usually provides sufficient relaxation and cooperation to allow an esophagoscopy examination to be made in a well ordered physician's office. It need not be a hospital procedure since sterile precautions are only necessary to prevent spreading of infection from one patient to another. Withal, esophagoscopy is a very valuable procedure which should not be neglected as a diagnostic aid.

It is not out of order at this point to call attention to a very useful diagnostic procedure that has not been very freely publicized. I have in mind the passage of olive-tipped bougies guided by a thread swallowed the previous day. A wise selection of sizes in the hands of one well acquainted with the sensations that should be encountered in the normal esophagus, furnishes an extremely useful means of making a differential diagnosis between cardiospasm and a carcinoma at the cardiac end of the stomach impinging upon the lower portions of the esophagus. Rarely does one encounter a true cardiospasm that will not admit of free passage of a No. 60 (French size) olive tip. On the other hand, one frequently finds cases of esophageal obstruction due to neoplasms at the cardiac end of the stomach which will not admit of the passage of any size. Such a procedure assumes greater importance when one realizes that this is one of the few neoplasms allowing the development of rather wide dilatation of the esophagus, closely resembling cardiospasm. Thus, while such an examination is not of paramount importance, it is, in its proper place, a very helpful aid.

The use of harsh, sharp and rigid, unguided sounds and bougies, curved forceps and Kelly clamps to explore the pharynx and upper esophagus is mentioned here only to be condemned. More than one patient has appeared for esophageal consultation with the mucous membrane badly traumatized following a night session in the emergency room in a futile hunt for a fish bone or common pin which had already left the esophagus in one direction or the other. Blind exploration of the esophagus is mentioned only to be condemned.

In 1933, Dr. E. B. Freeman casually recalled to mind the fact that during endoscopic observation of the cardiac sphincter we had both remarked that this seemed to open and close synchronously with the respiratory movements. This led to the conclusion that, provided we could momentarily interrupt the respiratory cycle at the exact instant when the cardiac opening remained closed, it would be possible, with the aid

of opaque media and fluoroscopic observation to outline the normal, unobstructed esophagus. Our conjecture proved to be correct and it was found that if opaque material was swallowed while forced expiration was maintained, an excellent outline of the normal esophagus could be obtained in a large number of individuals and recorded on an X-ray film. Specifically, the procedure was found to function perfectly in the large majority of asthenic, long-chested individuals. A large number of failures were noted in stout individuals having wide costal angles. A few failures were due to lack of cooperation or inability to carry out instructions but the greater portion were specifically due to an apparent inability of the cardiac opening to remain closed during the maintenance of forced expiration.

Our presentation concerning this procedure was read before the Radiological Society of North America in December, 1933. We had hoped to stimulate interest in this procedure among the Radiologists but it provoked very little discussion. I wish to show lantern slides of this procedure at the end of this discussion including one made of the partially obstructed esophagus. In this instance, the procedure seemed of no value because the opaque material trickled through too slowly for a satisfactory film to be taken. However, the procedure is not recommended for the obstructed or partially obstructed esophagus. We think it to be particularly useful in cases of benign tumors of the esophagus, esophageal varices and peptic ulcers of the esophagus. I should welcome a frank discussion on the usefulness of this procedure.

In appealing for a more widespread interest in diseases of the esophagus, I have but a few suggestions to make. I know that you are all interested in the early diagnosis of esophageal disease. I know that you are all familiar with the more common symptoms of esophageal disease. I am well aware that few patients today, die of chronic cardiospasm. This is as it should be. Education, enlightenment and fairly early diagnosis have contributed mightily to this happy result. On the other hand, few, if any, carcinomas of the esophagus survive. This is not as it should be. I do not believe the situation is so entirely hopeless. I am confident that some day, someone is going to devise a suitable operation for the removal of malignant esophageal tumors or that suitable methods of radiation therapy and surgical management will be evolved.

The best treatment thus far devised, for a malignant stricture of the esophagus is either often repeated dilatation or gastrostomy, neither of which offers the sufferer much solace. Since carcinoma of the esophagus usually provokes symptoms very early and because metastases often occur reasonably late, either procedure nearly always contributes to an amazingly longer life than is allowed almost any other untreated carcinoma patient. It is debatable then whether such palliation actually may not bring about a prolongation of an already miserable state. To date, very few esophageal carcinomas have been cured by surgery. But, over a period of years, we have seen several patients almost survive various radical surgical procedures. One case, in particular, lived three weeks following operation and died from a pneumonia infection. Such cases are disappointing but should not be entirely disheartening. In view of these facts, I

am earnestly asking, therefore, that distinguished groups of physicians such as this, diligently publicize this condition among their fellows in order to bring patients earlier to the proper treatment and especially try to interest surgeons in order that they may be persuaded to devise a type of operation which will assure survival, at least in a certain percentage of cases.

DISCUSSION

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): My experience agrees with that of the speaker in regard to the frequent occurrence of pain before the onset of dysphagia. It is remarkable how the location of both the pain and the dysphagia is usually directly opposite the site of the lesion.

In regard to X-ray diagnosis, the marking of spot films during fluoroscopy is of the greatest help in studying the details at a point of narrowing. It is well to emphasize the importance of ruling out the presence of an aneurysm before passing any stiff bougie, even though it is passed over a string as a guide. On the other hand, a Rehfuess tube is safe to pass and occasionally I have been able to recognize early carcinoma of the esophagus because the tip of the tube would not pass that point and bloody mucus was obtained by aspiration. In cardiospasm, after the tube has been allowed to remain for a considerable length of time, it may suddenly pass through into the stomach. These observations emphasize the importance of having the clinician himself pass the stomach tube instead of leaving it to a technician or nurse.

DR. ELMER B. FREEMAN (Baltimore): Mr. President, one point I particularly want to stress that Dr. Wright brought out in his paper is the use of bougies when passed over previously swallowed thread as a guide. It is a very valuable procedure in the differential diagnosis between chronic cardiospasm, and malignancy occurring in the cardiac end of the stomach that is encroaching upon the cardia. In this group of cases esophagoscopy fails to show an obstructive lesion in the lower end of the esophagus, but the obstruction can easily be located by passing properly guided bougies. It has been my experience that a number sixty French scale bougie can be readily passed in all cases of chronic cardiospasm. If a number sixty bougie does not readily pass through the cardia in a suspected case of chronic cardiospasm, it will usually be found that the obstruction to the cardia is due to malignancy in the cardiac end of the stomach encroaching upon the lower end of the esophagus.

DR. WILLIAM A. SWALM (Philadelphia): As I listened to this paper on Esophageal problems, I thought it would not be amiss to mention the experimental studies of Dr. Lester M. Morrison and myself in this field. Balloons were distended at various levels of the esophagus in patients with functional (angina pectoris) and organic cardio-vascular disease. In several of the cases, complete temporary stoppage of the heart was produced, coronary artery (S-T electrocardiographic inversions) changes and multifocal extra-ventricular systoles and arrhythmias were caused. Syncope and substernal distress could easily be produced. It is important to bear these facts in mind in cardiac cases where various diagnostic techniques and investigations of the esophagus are carried out. Serious and even fatal accidents may occur indirectly through the heart in cardiac cases by vago-vagal reflex, and the gravest caution must be exercised.

DR. JOHN H. FITZGIBBON (Portland, Ore.): I should like to make a suggestion as to technique. Dr. Wright mentioned the difficulty of outlining the lower limit of the stricture in cases of tumor of the esophagus. I have been able to outline the lower limit fairly accurately in most cases of carcinoma by having the patient take barium

while lying down, swallowing on the level or uphill. This is allowed for barium to pass through the stricture, and settle at the lower end. If Dr. Wright will follow that method with his breathing technic, he will be able to outline most growths.

DR. B. B. VINCENT LYON (Philadelphia): Mr. President and Fellow Members: In 1916 I published a paper on cardiospasm (Am. J. Med. Sc., March, 1916, Vol. 151, p. 389). I reported a chronic case who recovered by methods of treatment that I would no longer want to endorse because therapy has since improved. But I learned certain points in differential diagnosis of esophageal lesions that have not yet been mentioned in this discussion.

I. Some cases of chronic cardiospasm present clinical signs and symptoms that strongly suggest bronchiectasis. But the differential diagnosis can be made by X-ray, by stomach tube and by examination of material recovered.

II. As Dr. Andresen has just pointed out, the doctor can frequently get a quick clinical impression of an esophageal lesion by sense of touch, by failure of the stomach or duodenal tube to readily enter the stomach—it meets with an obstruction. Doctors should teach nurses and technicians to report promptly such an instance to the doctor. But I think a differentiation between cardiospasm and carcinoma can be made by the third point, namely.

III. In my experience, if one watches the flow of water or lavaging solution through the glass percolator, in the cardiospasm case one will notice that the water may flow in evenly for a few centimeters, then as the spasm occurs, the level of water will stop and oscillate, perhaps for several seconds, and as the spasm relaxes, smooth flow will recur for a few centimeters, and so on. In most of my carcinoma cases, even those approaching total stenosis or stricture, there is usually sufficient channel remaining to allow the esophageal lavaging fluid to enter the stomach evenly although more slowly.

Also in gastric lavage, either with stomach or duodenal tube, by similarly watching and timing the rate of inflow and outflow, one may distinguish between the atonic and hypertonic stomach. In the latter when gastric spasm occurs it increases intragastric tension and this, in turn, produces fluctuations in inflow and outflow not seen in normal subjects. For further details, those interested might consult p. 309, "Non-Surgical Drainage of the Gall Tract" (Lea and Febiger).

DR. EDWARD B. BENEDICT (Boston, Mass.): I should merely like to mention in regard to esophageal surgery that we have now at the Massachusetts General Hospital two patients who have had esophagectomy by Dr. Churchill for carcinoma of the thoracic esophagus. In both of them I obtained a positive biopsy of epidermoid carcinoma by esophagoscopy. One is now doing well five months after removal of the esophagus; the other is only three weeks postoperative, doing fairly well.

DR. HAROLD E. WRIGHT (Baltimore): I am greatly appreciative of the manner in which this slight presentation has been accepted, and I am very glad that I had the opportunity to present this particularly because I have learned a great many things.

In regard to the presence of aneurysm and cardiac disease, in manipulation of the esophagus, I neglected to state we are always very careful to determine the presence of aneurysm or dilated aorta before we attempt any intrasophageal procedures, and I am not so sure that I would attempt any procedures in the presence of even cardiac disease, that is, procedures I have mentioned.

Dr. Benedict's statement about his two patients is very encouraging to me. I was glad to hear that—and that was the principal point in my presentation, i.e. to stimulate interest in these hopeless patients with carcinoma of the esophagus.

Gastritis Simulating Tumor Formation

By

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THE purpose of this paper is to present seven instances in which gastritis simulated neoplastic infiltration. In these cases the diagnosis of gastric tumor was made either at X-ray examination or at gastroscopy or at surgical operation, but the microscopic examination disclosed some type of chronic gastritis. Similar cases have been described by Brunn and Pearl (1), Konjetzny (2), Moutier (4), and others (6), and considered to be rare. However, I have observed seven such cases within a relatively short time, and therefore believe that they occur rather frequently.

Case 1. A thirty-five year old salesman was first seen on December 12, 1935. He died from Hodgkin's disease in November, 1938, the time of observation being three years. About three years before admission he had begun to experience slight pain in the epigastric region with heart-

rous neoplasm of the pyloric end of the stomach." The findings at the first gastroscopy (December 30, 1935) were most unusual. The mucosa of the angulus and the antrum was tremendously thickened and stiff; the musculus sphincter antri was about three times its normal size. In this infiltrated area, superficial ulcerations of different size and irregular shape were seen. The impression was that the infiltration of the angulus might be gastritis, but that malignancy or syphilitic infiltration could not be excluded. Neoplasm was considered to be unlikely only after the third gastroscopic examination, forty-three days later. The ulcers had healed at this time, but other superficial ulcers had developed. The wall of the antrum was nodular, elevated, and stiff. A malignant infiltration, then, seemed unlikely because the parts previously involved were now healed. An atypical form of ulcerating hypertrophic gastritis was diagnosed. On May 23, 1936, this diagnosis was adopted by the roentgenologist. The patient, who had

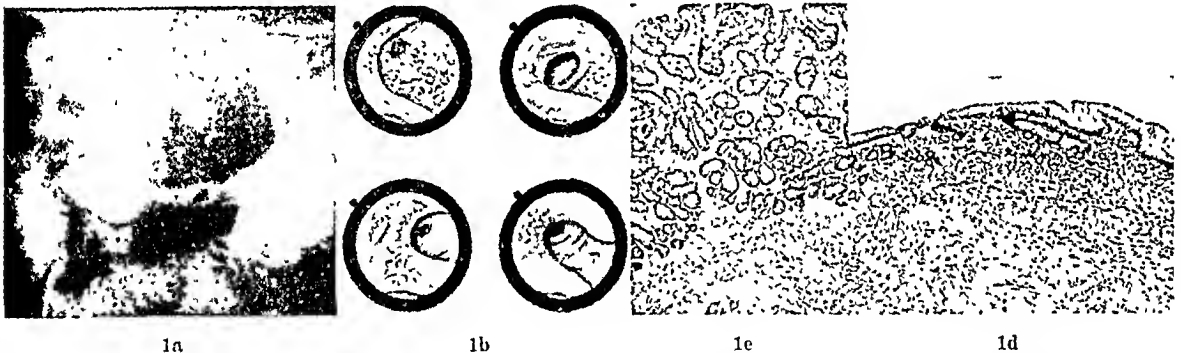


Fig. 1, Case 1. *Chronic hyperplastic atrophic ulcerative antrum gastritis* in a patient who 3 years later died from Hodgkin's disease. (a) X-ray picture of the stomach taken on 12-19-35, simulating pyloric carcinoma. (b) Gastroscopic views as seen on 9-27-36, 11-22-36, 12-10-37 and 1-17-38. From December, 1935, to December, 1937, the picture was essentially the same: Thickened mucosa with formation of nodules and multiple ulcerations was seen in the antrum and in the musculus sphincter antri. On 1-17-38, atrophy of the antrum mucosa was observed. (c) Biopsy, taken in April, 1938, from the greater curvature of the antrum: Severe atrophic gastritis. The glandular apparatus has almost disappeared. The surface epithelium, the crypts and the remnants of glands are lined by an epithelium containing many goblet cells. (d) Microscopic section through the same region as pictured in (c) as found at post mortem examination: the gastric mucosa now is entirely atrophic, the surface epithelium almost touching the muscularis mucosae.

burn. This was not related to meals. The pain became gradually more severe. Ulcer management gave him only temporary relief. He was nauseated and vomited. The appetite was fair. At admission at Billings Hospital, eight months later, the physical examination was essentially negative. Repeated histamine tests showed an acidity between 68 (in 1936) and 18 (in 1938); the benzidine reaction in the stool was negative to 4+; eighteen X-ray examinations of the stomach and twenty-three gastroscopic examinations were carried out. The first X-ray examination, on December 19, 1935 (Fig. 1a), revealed definite evidence of gastric disease. In all of the views a frank filling defect could be made out in the pyloric antrum. The radiologist concluded his report as follows: "It is hard to escape the conviction that the patient has a small seir-

followed an ulcer diet, was feeling fine at that time and had almost no distress. He remained in this excellent subjective condition until March, 1938. Objectively, however, the most severe changes were seen at repeated gastroscopic examinations. The width and infiltration of the antrum pylori varied, but always nodules and ulcerations were found (Fig. 1b). In December, 1937, the picture changed suddenly. The antrum mucosa had become gray in color, smooth and thin. A marked atrophy developed. At X-ray examination, also, marked improvement was noted. In April, 1938, fever developed, a retroperitoneal tumor was felt, and a laparotomy was performed. Biopsies from the tumor, as well as from the greater curvature of the gastric antrum, were taken. The tumor proved to be a typical Hodgkin lymphogranuloma. In the stomach section, in accordance with the gastroscopic picture, atrophic gastritis was found (Fig. 1c).

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This ntrophy progressed rapidly. When the patient died, the gastric wall was found to be entirely free of Hodgkin's disease, but the atrophy now was complete (Fig. 1d).

COMMENT

In a thirty-five year old male complaining of epigastric distress at X-ray, gastric carcinoma was diagnosed; at gastroscopy, ulcerative antrum gastritis was assumed, but malignancy could not be ruled out. The course proved that an unusual type of ulcerative gastritis was present which later turned into atrophy. The patient died three years later from Hodgkin's disease. At autopsy, the possibility of gastric Hodgkin lymphogranuloma was seriously considered, but the pathologist was unable to find any trace of it. Only severe atrophy of the gastric mucosa was found.

Case 2. A thirty-seven year old lady had been under the care of Dr. C. Burborkn for several yrs. I am indebted very much to him for the clinical data of this period.



Fig. 2. Case 2. Chronic hyperplastic atrophic ulcerative antrum gastritis simulating polyposis by X-ray and carcinoma at gastroscopic examination. (a) X-ray picture. The dark round filling defects simulate polyposis. (b) gastroscopic picture: Stiffness of the mucosa with formation of nodes and superficial ulcerations simulates carcinoma. (c) Microscopic section through the largest of the ulcerations. The ulcer does not penetrate through the muscularis mucosae. The mucosa presents atrophy, formation of cysts and compensatory irregular proliferation. There is tremendous lymphocytic infiltration. (d) Right edge of the ulcer demonstrated in c, seen under higher power. The pseudopolyps are inflammatory products, containing many plasma cells.

When she first consulted him, she gave the history that she had had occasional vomiting for seventeen years, and that normal amounts of food caused fullness and distension of the abdomen. She had induced vomiting after meals because she had the obsessional desire to be underweight. Her daily intake of protein averaged 20 to 30 grams. There was a typical severe nutritional edema and she was anemic. Following the institution of a high protein, adequate, well balanced diet, the edema disappeared and the anemia improved. Many months later, when she was seen first at Billings Hospital, she stated that she had been subject to brief spells of epigastric pain. X-ray examination (Dr. F. Templeton) revealed a picture highly suggestive of gastric polyposis (Fig. 2a). He urged gastroscopic examination, and the patient underwent four gastroscopies in the following three weeks. At first, retention of food prevented a definite diagnosis. Then the following was reported: The region of the angulus and the antrum appeared to be thickened and nodular. The nodes were broad-based and did not look like polyps. In the pos-

terior wall above the ngulus a gray, shallow, oval ulceration was observed. Another one was present at the lesser curvature of the antrum. At the side of this second gray area, a dark red node was seen. There was no boundary between the infiltrated area and the normal mucosa (Fig. 2b). The mucosa of the upper portions of the stomach was velvety, containing crevasses and red spots. The impression was: "Ulcerative infiltrative process of the antrum, probably carcinoma with ulcerations." But other types of infiltrative lesions could not be ruled out. Free HCl after histamine went up to 28; no occult blood was found in the stools. Gastric resection, because of pyloric obstruction, was performed by Dr. L. Dragstedt. The pyloric antrum felt diffusely thickened, but there was no evidence of carcinoma. In the gross specimen, the entire mucosal surface of the antrum was covered by small and large nodules and verrucae, absolutely identical with those seen at gastroscopy. Two of these nodes were dark red. Numerous microscopic sections were made, none of them revealing any trace of carcinoma. A severe inflammation

was found. Cellular infiltration and edema was observed in the mucosa, the muscularis mucosae, and submucosa. The ulcerations did not penetrate the muscularis mucosae (Fig. 2c). Proliferative inflammatory nodes and pseudopolyps were found consisting of granulation tissue with many plasma cells (Fig. 2d).

COMMENT

A thirty-seven year old lady had been suffering several months, prior to admission, from nutritional edema and protein deficiency. At admission she complained of rather mild epigastric distress. At X-ray, polyposis was diagnosed; at gastroscopy, infiltrative carcinoma appeared to be the most likely diagnosis. Pyloric obstruction led to surgery, and atrophic hyperplastic antrum gastritis was found. Since in these rare cases almost invariably carcinoma later develops, resection would have been indicated, even if no obstruction would have been present.

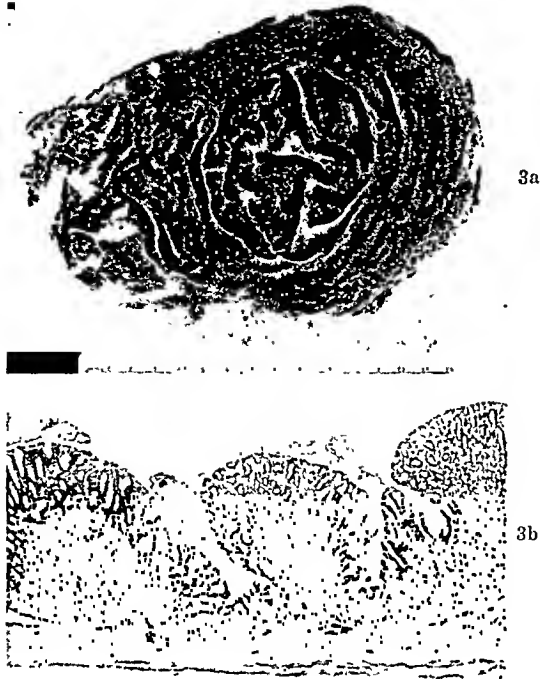


Fig. 3, Case 3. *Localized hypertrophic gastritis, simulating carcinoma.* (a) Gross specimen containing an elevated area of stiff nodular infiltrated folds. (b) Microscopic section through the elevated area seen in (a). Irregular hypertrophy and proliferation of the gastric mucosa. Cellular infiltration.

Case 3. In this case, the wrong gastroscopic diagnosis of gastric carcinoma instead of hypertrophic tumor simulating gastritis, led us to resection with fatal outcome. Konjetzny (2) believes that in such cases resection is always indicated, but I believe it would be better to treat such patients conservatively. Therefore, the difficulty of this differential diagnosis should be emphasized. X-ray examination in a seventy-one year old man complaining of gas in the stomach revealed markedly enlarged rugae suggestive of gastritis, in December, 1936. The acidity was 42 at the histamine test; the benzidine reaction was positive. The gastroscopic impression was: unexplained bulging of the greater curvature which may be (a) extra-gastric mass, (b) unusual form of submucosal carcinomatous infiltration, (c) unusual form of tumor-like chronic inflammatory infiltration. From 1937 to September, 1938, the patient lost twenty-three pounds, had a poor appetite, and continuous epigastric pain. At gastroscopy, a large protrusion of the posterior wall was seen covered by mucus and fresh blood. There was no sharp limit, and I decided to call this a definite carcinoma. The diagnosis was wrong. The surgeon felt, at laparotomy, large papillomatous folds and decided to carry out a resection. In the gross specimen (Fig. 3a), there was a large area, at a distance of 7 cm. from the pylorus in the greater curvature and posterior wall, 8 cm. x 7 cm., made up of concentric mucosal folds which varied from 1½ cm. to 3 cm. in height. Microscopic examination revealed the typical picture of a severe localized hypertrophic gastritis: irregular hypertrophy, deepening and cork-screw formation of the crypts, interstitial infiltration, and some small cysts (Fig. 3b). The patient died from the operation. The

shallow ulcer seen at gastroscopy was found at the post-mortem examination.

COMMENT

In a seventy-one year old patient at X-ray and at gastroscopy, an infiltration was found suggestive of gastritis; but, at gastroscopy, carcinoma was not excluded with certainty. The condition of the patient became worse within one year, and after a repeated gastroscopic examination, the diagnosis of a gastric carcinoma was made. The surgeon, also, was unable to exclude carcinoma and made a resection, following which the patient died. Microscopic examination revealed severe hypertrophic tumor simulating gastritis. The resection, in this case, would have been avoided only, if before, a biopsy would have been taken and examined microscopically. (See later).

Case 4. A similar case was seen by Dr. H. Brunn of San Francisco, to whose courtesy I owe the anatomical material. Brunn and Pearl were the first to describe tumor simulating hypertrophic gastritis (1). This patient had had severe attacks of pain, nausea, and vomiting of blood. At X-ray, an extensive polypoid carcinoma was diagnosed. Dr. Brunn, at laparotomy, opened the stomach, found a thickened mucosa, and decided to make a resection. The gross specimen shows a tumor-like thickened mucosa (Fig. 4a). The microscopic sections contain proliferation of the mucosa, many large cysts (Fig. 4b) and mucosal hemorrhage.

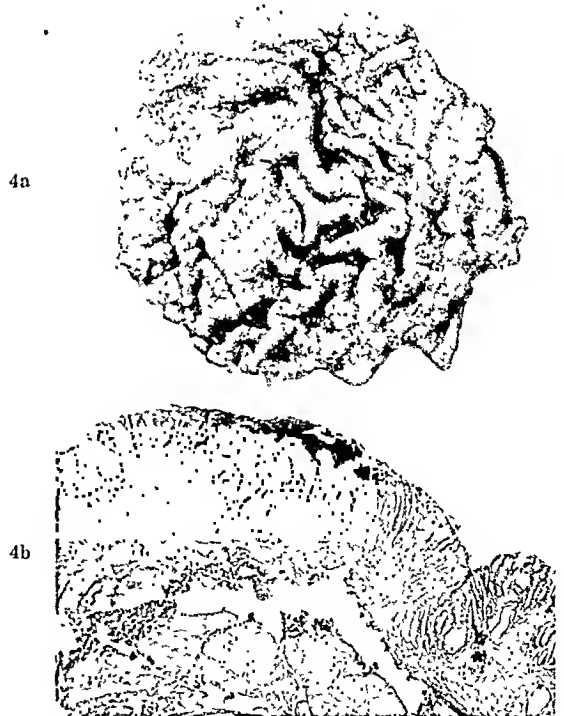


Fig. 4, Case 4. *Diffuse chronic hypertrophic gastritis simulating carcinoma.* (a) Gross specimen. The gastric mucosa is tremendously thickened and contains thickened nodular folds. (b) Microscopic section through the gastric wall: There is irregular proliferation, the crypts are elongated, cork-screw-like or even transformed into large cysts. One area of these cysts is covered by a fresh inflammatory hemorrhage. (Courtesy of Dr. H. Brunn, San Francisco).

COMMENT

At X-ray examination and at surgical operation, gastric carcinoma was diagnosed, while the microscopic examination revealed severe hypertrophic cystic gastritis.

Case 5. This forty-six year old man was referred, by Dr. Ralph Brown, for gastroscopic examination because, at X-ray examination, a tumor mass of the fundus had been found. At gastroscopy, swollen, tortuous, edematous folds were observed, and a protrusion of the anterior wall and lesser curvature was seen (Fig. 5a). I thought this was due either to an extragastric tumor or to an unusual form of tumor-simulating gastritis. This latter diagnosis proved to be correct at operation. The surgeon opened the stomach and found a very thick and hypertrophied mucosa; there were rugae as much as two to three inches

observation and to whose courtesy I owe the material. At gastroscopy, a tumor of the posterior wall of the antrum was seen. A resection was carried out. Macroscopically, nothing abnormal was seen. Microscopic examination revealed the presence of a foreign body granuloma. Pieces of knolin the patient had taken had invaded somehow the gastric mucosa and had effected this unique inflammatory granuloma.

COMMENT

A foreign-body inflammatory granuloma simulated gastric tumor at gastroscopy.

Case 7. A sixty-three year old man had loss of appetite, loss of weight (twenty-five pounds), epigastric distress, and gas on the stomach for six years. Physical, laboratory, and X-ray examination were entirely negative. (The free acidity at the histamine test was 67). But, at gastroscopy,

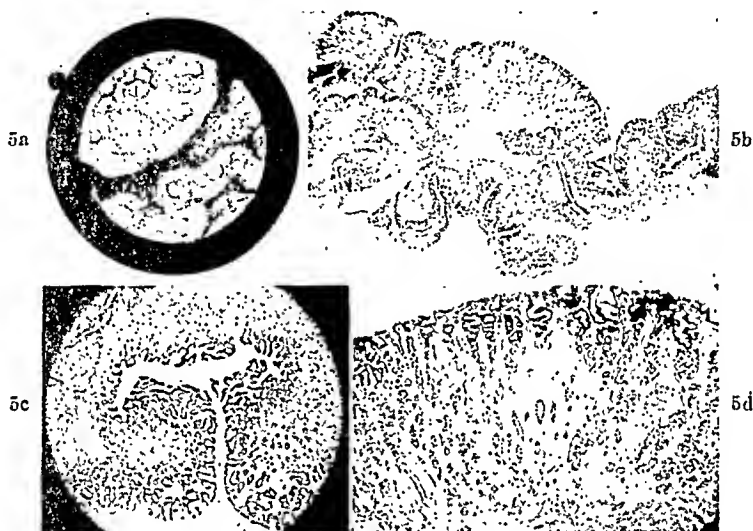


Fig. 5, Case 5. *Severe hypertrophic gastritis, simulating tumor at X-ray examination.* (a) Gastroscopic view. There is an edematous tumor mass in the left upper quadrant which at gastroscopy was believed to be either extragastric tumor or severe hypertrophic gastritis. The folds are swollen, tortuous and edematous. (b) Microscopic section through a biopsy of the gastric wall. Survey, demonstrating the grotesque proliferation of the gastric mucosa. (c) Part of b, seen under higher power and demonstrating the proliferation of the mucosa with formation of polyplike islands. (d) Part of b, seen under higher power, demonstrating the corkscrew-formation of the crypts and the severe edema which had been seen gastroscopically. (Courtesy of Dr. Ralph Brown, Chicago).

high. Almost the entire small bowel and some portions of the large bowel also were involved in this hypertrophy. This fact would let us think of some unknown congenital hypertrophy. However, a biopsy was taken, and microscopic examination revealed the inflammatory character. (Fig. 5b-d). There was grotesque fan- and polyp-like proliferation with elongation and cork-screw formation of the crypts, extensive edema, some infiltration, and formation of polypoid islands.

COMMENT

In this case, gastric tumor was diagnosed at X-ray examination. At gastroscopy, the diagnosis of tumor-simulating gastritis was made tentatively. Microscopic sections of a biopsy revealed a most unusual form of tremendous hypertrophic gastritis.

Case 6. This case will be reported extensively by Dr. Allan Cohn of San Francisco, who made the gastroscopic

very definite pathological picture was seen. Three gastroscopic examinations were carried out. Since a definite infiltrative lesion had been observed, its demonstration by X-ray was tried again, but in vain. With the finest relief examination the stomach appeared to be normal. The protocol of the third gastroscopic examination read as follows: "Again very marked and severe changes were seen. The antrum appeared quite normal. The musculus sphincter antri was thickened and stiff. Above it on the anterior wall close to the greater curvature again an area was seen in which the mucosa looked stiff and contained many ulcerations. These ulcerations were gray in color, two of them were large; about five or six were rather small. They were partly confluent, but their edges were nevertheless sharp. The anterior wall toward the lesser curvature at the same level looked a little bit thin. The posterior wall (Fig. 6a), from the midportion of the stomach up to the fornix, was stiff and contained many

irregular nodes and nodules, the tops of which appeared to be reddened. On the posterior wall of the fornix irregular ulcerated areas were seen. Impression: There is no doubt that there is a hyperplastic ulcerative lesion of the posterior wall and of the lower portion of the greater curvature and anterior wall. I do not know what kind of lesion this is. The picture is entirely unusual for hypertrophic gastritis but, since peristaltic waves were seen passing over this area by fluoroscopy, the possibility of this type of lesion must be born in mind. An infiltrative malignancy is somewhat more likely from a purely statistical standpoint. Other infiltrative lesions cannot be ruled out. In my opinion, the safest procedure would be to open the abdomen, take out a piece of the upper posterior wall for biopsy, and then eventually institute X-ray therapy." This was done. The surgeon, at operation, felt an entirely normal stomach; he was not able to feel either the infiltration seen so exactly at gastroscopy or the ulcerations. The biopsy from the posterior wall was made, and microscopic observation revealed a quite unusual picture (Fig. 6b). The mucosa was almost completely atrophic,

picious posterior wall, the idea of some kind of gastritis was conceived. A biopsy was taken although at operation nothing at all was felt. This biopsy revealed a very unusual picture of dense lymphocytic infiltration of the atrophic gastric mucosa. The failure of X-ray therapy to improve the gastroscopic picture suggests that this is a "lymphoblastomoid" atrophic gastritis rather than a lymphoblastoma.

DISCUSSION

In seven cases, great difficulties were experienced at X-ray examination or at gastroscopy or during the surgical exploration to make the differential diagnosis between gastric tumor and gastritis. Microscopically, in these cases, unusually severe gastritis of different types was found, sometimes typical hypertrophic gastritis, but also atrophic gastritis with compensatory hyperplasia or lymphocytic infiltration. However, in all of these cases the picture found was an unusual



Fig. 6, Case 7. *Lymphoblastomoid atrophic gastritis* (Lymphoblastoma?) At the gastroscopic examination the differential diagnosis between carcinoma, lymphoblastoma, Hodgkin and gastritis was impossible. Neither at X-ray examination nor at palpation during the operation any kind of pathology was found. (a) Gastroscopic picture. Infiltration causing acute bleeding in the left upper portion; formation of shallow erosions in the right upper portion; atrophy in the lower portion. (b) Microscopic section through a biopsy of the upper posterior wall of the stomach. The glandular apparatus of the mucosa is almost completely replaced by a tremendous lymphocytic infiltration.* The differential diagnosis between lymphoblastoma and "lymphoblastomoid" atrophic gastritis is not possible with certainty.

*and one erosion.

the glands had disappeared completely, but a tremendous lymphocytic infiltration was found. Some erosions were seen. The opinion of the pathologists concerning the microscopic diagnosis was divided. Most of them were inclined to diagnose a real lymphoblastoma, but also the diagnosis of an unusual form of chronic gastritis was made. The patient then received X-ray therapy, and was reexamined several times gastroscopically. True lymphoblastoma reacts rapidly to X-ray therapy (5), but in this case no definite improvement was observed. Repeatedly, infiltration, ulcerations and atrophy were seen. The patient felt fine, was free of symptoms, and gained weight. Histamine-proved anacidity developed due probably to the radiation therapy (2878 R). I believe that this is a case of "lymphoblastomoid" atrophic gastritis, but sufficient time has not yet elapsed to prove this diagnosis.

COMMENT

In a man in whom physical examination, laboratory methods and X-ray had been entirely negative, gastroscopy revealed infiltration with ulcerations suggestive of carcinoma. When repeated X-ray examination showed peristaltic waves migrating over the sus-

one, and all examiners realized the diagnostic difficulties. The question comes up as to what to do if we encounter this type of diagnostic difficulty. If there is pyloric obstruction, immediate resection is indicated. The same is true if there is an isolated polypoid gastritis of the antrum present, since there is unanimity that this condition probably invariably leads to the development of gastric carcinoma. Konjetzny believes that in every case of tumor-simulating gastritis resection is indicated, but this seems hardly justified. The fatal end of our Case 3 would have been avoided by conservative treatment based on a correct diagnosis. Such cases probably can be treated medically with safety. However, if there are diagnostic doubts, the method used in Cases 1, 5 and 7 can be recommended strongly: namely, to take first a biopsy from the suspicious area. This is a rather safe procedure. The examination of frozen sections of the gastric wall during the operation usually will be unsatisfactory, and therefore resection should be delayed until thorough microscopic examination has proved the

presence of carcinoma. Microscopic study will suggest either resection (in the case of carcinoma) or X-ray therapy (in the case of lymphoblastoma or Hodgkin's disease) or antisiphilitic treatment (in the case of gastric syphilis) or conservative treatment (in the case of chronic gastritis). The frequency of gastritis simulating tumor formation should not be underestimated.

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DISCUSSION

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): I shall presently show three slides illustrating three of my own recent cases which corroborate Doctor Schindler's observations. Of immediate concern to us are those polypoid gastric lesions, irrespective of their size or number, because of their relative frequency and potentiality for carcinomatous transformation. In the preparation of a recent article on benign gastric tumors I had occasion to tabulate the number of such lesions observed at the Mayo Clinic up to the present time. It will be recalled that Balfour and Henderson reported a series of fifty-eight cases in 1927. The number has grown to 176, exclusive of those found at autopsy, and more than 45 per cent of these are patients with adenomatous polyps. Many of these are multiple.

The role that gastritis plays in the genesis of such polypi is still a matter of controversy. Polypoid forms of gastritis have much in common with the adenomatous polyps, especially the smaller multiple ones. Differential diagnosis is often dependent on gastroscopic and microscopic examination.

The first slide is of historical interest and was reproduced from an illustration in Faber's excellent monograph "Gastritis and its consequences." It is a postmortem specimen of diffuse hypertrophic polypoid gastritis involving the entire stomach. Curiously enough, this condition gave rise to no gastric symptoms during the life of the patient.

The second slide represents the gastric pathology of a man fifty-seven years of age, who for a year and a half prior to admission had indigestion of progressive severity in addition to marked loss of weight and strength. His distress appeared right after meals and was unrelieved by the usual measures. He had a persistent achlorhydria even after stimulation with histamine. Roentgenologic examination was essentially negative but more careful study of the mucosal relief suggested the presence of a gastritis. Gastroscopic examination disclosed what you actually see, namely, a marked hypertrophic gastritis with frank polypoid formation. Unfortunately the patient had a pulmonary embolism following surgical exploration, but this gave us an opportunity to get a complete stomach as a specimen and the necropsy findings substantiated the gastroscopic diagnosis.

The third slide depicts the characteristic defects as revealed on the roentgen-ray film. This patient had no symptoms other than gross bleeding from time to time. Early carcinomatous transformation of these polypi had already taken place.

DR. CHESTER M. JONES (Boston): I should like to ask Dr. Schindler what he thinks the connection is be-

tween this peculiar polyposis of the stomach and that which we see occasionally in pernicious anemia.

I recall several patients, one in particular, where operation seemed indicated because of the suggestion that one of the large polypoid growths was ulcerated and, at operation, the largest one of the polypoid growths was removed and turned out to be carcinomatous.

Almost the entire stomach was so covered with diffuse very striking thickening, it was difficult to choose what portion of the stomach to resect. The patient was not in condition to do a complete resection at that time; as a matter of fact, this patient had pernicious anemia, and we have observed him for a period of over four and a half years. There has been a continual improvement in the appearance of the gastric mucous membrane since the original operation.

I am sure that he did have a curious polypoid type of gastritis and one of the projections did become carcinomatous. We have had two or three others that fitted into this scheme, I think, rather well.

DR. JOHN L. KANTOR (New York) showed three slides of giant rugae that were mistaken for carcinoma. Differential diagnosis was made at laparotomy.

DR. MAURICE FELDMAN (Baltimore): Dr. Schindler is to be complimented for reemphasizing this form of gastritis. These cases offer considerable difficulty at times.

The neoplastic forms of gastritis may be produced by certain forms of alcoholic gastritis, hypertrophic ulcerative gastritis, and corrosive gastritis.

Hypertrophic ulcerative gastritis is a rare form of this infection. It produces a roentgen picture resembling carcinoma, from which it is difficult to differentiate. The wall of the affected segment of the stomach, usually the pylorus portion, is greatly thickened, produces a neoplastic type of defect. On fluoroscopic examination the inflammatory mass often can be readily felt. The mucosal folds are markedly thickened and reduced in number. The differential diagnosis is made by the presence of mucosal folds.

Corrosive gastritis also produces a neoplastic inflammation, ranging from a superficial hemorrhagic necrosis to a marked shrinking of the whole stomach. The roentgen examination shows a rigid, markedly swollen mucosa, the size of the stomach is often greatly reduced, and the scar formation often leads to stenosis and pipe-like deformities of the pylorus.

In the neoplastic form of alcoholic gastritis, the stomach is greatly reduced in size, of smooth contour, empties with marked rapidity, and has all the characteristics of other varieties of linitis plastica.

I should like to show these three varieties on the screen.

(Slide) Here is a case of chronic alcoholic gastritis, showing a typical linitis plastica with smooth walls and extremely rapid emptying of the stomach.

(Slide) A case of ulcerative hypertrophic gastritis, showing involvement of the pylorus and antrum, and two ulcer filling defects at operation proved to be a case of hypertrophic gastritis.

(Slide) Another case of hypertrophic ulcerative gastritis. Operation revealed several ulcers and a large defect in the pyloric antrum. An inflammatory mass corresponding to this defect, was felt to roll under the palpating hand.

(Slide) A case of corrosive gastritis in which a linitis type of stomach is present. Note the pipe-like deformity of the pylorus, and the two ulcer defects on the lesser curvature.

DR. LEON SCHIFF (Cincinnati, Ohio): Mr. President, Members and Guests: I feel that Dr. Schindler's communication is very important and timely and would like to show two slides in connection with it.

(Slide) This was taken from a patient with pernicious anemia in relapse, who presented this persistent defect in the lower end of his stomach. It was thought to be carcinomatous, but because of the reports of French observers

of pseudo-defects due to edema of the gastric mucous membrane, occurring in cases of pernicious anemia, operative interference was deferred. Gastroscopic examination revealed slight nodular infiltration of the antrum suggestive of hypertrophic gastritis. The patient responded characteristically to anti-anemic treatment, but the X-ray defect persisted. He was therefore operated, and hypertrophic gastritis was found to be present.

(Slide) This is a photograph of a drawing made post-mortem of the stomach of a patient with clinical and roentgenological findings characteristic of gastric carcinoma. However, because of these enormous rugae, a diagnosis of hypertrophic gastritis was made on gastroscopic examination. Microscopic sections, to our surprise, revealed carcinomatous infiltration throughout the large rugae.

These two cases, therefore, show that not only may gastritis simulate carcinoma but conversely that carcinoma may simulate gastritis.

DR. EDWARD B. BENEDICT (Boston): We have had the same experience at the Massachusetts General Hospital that Dr. Schindler speaks of, in differentiating hypertrophic gastritis from carcinoma in several cases, but, by carefully evaluating the clinical history, X-ray and gastroscopic findings, I don't think we have made very many mistakes.

In the following case, however, we all made a mistake: A woman of forty-five complained of anorexia, vomiting and loss of sixty pounds in weight; when she came in she weighed only ninety-five pounds. The X-ray showed poor mucosal relief and the roentgenologist said, "If gastroscopy shows surface changes, the lesion is an infiltrating neoplasm." Gastroscopy did show a very nodular appearance with erosions. I felt the appearance was too nodular for gastritis alone. Operation showed an apparently normal stomach, but at my request the surgeon took a biopsy which was reported as chronic gastritis. He did a jejunostomy in this patient, with complete relief.

DR. A. C. IVY (Chicago): Since the question of etiology has been introduced by one of the discussers and

also by Dr. Necheles' presentation, I should like to point out that several years ago we produced in dogs a hypertrophy of the gastric mucosa and a superficial ulcerative gastritis in some instances, by injecting histamine at hourly intervals, and also pilocarpine. Histamine was injected with the idea of promoting a continuous secretion of free acid by the stomach, and pilocarpine with the idea of producing continuous spasm and motility of the stomach.

I mention this only to bring out the idea that a number of factors may be concerned in producing a gastritis.

DR. RUDOLF SCHINDLER (Chicago): I want to thank all speakers for their kind interest, and I am very glad that so many cases were reported which show that this condition is not a rare one and that the differential diagnosis between infiltrative lesions is a difficult one. We need to take the case history carefully and make a careful X-ray examination and a careful gastroscopic examination.

The one case of Dr. Feldman seems to me extremely rare. These things have been described in the French literature, but I never have seen such a case.

Dr. Schiff, I omitted the cases in which an error was made in the opposite direction. They occur; I agree with that.

Dr. Eusterman and Dr. Jones brought up a very important question which I think cannot be settled in the final word, namely, the correlation between polyps and carcinoma, and between true polyps and inflammatory polyps. There is a school, especially Toennesen, who think that there is no difference between inflammatory polyps and true tumors. I think we should try to draw this line definitely and I think we can do this. On the other hand, I believe that even the inflammatory nodular ulcerative antral gastritis may be a precursor of carcinoma and, therefore, I think in these cases we should advocate early resection.

Thank you very much!

The Characteristics of the Normal Human Gastric Secretory Curve, Using An Improved Gastric Test Meal

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and

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THE commonly used gastric test meals (bread, toast, arrow root cookies or shredded wheat biscuits with water or weak tea) are generally agreed to be far from satisfactory. The chief errors and deficiencies of the commonly used test meals may be briefly summarized as follows: *First*, their secretagogue content is low; hence they do not supply a maximal physiological stimulus for acid secretion. *Second*, the acid secreted by the stomach is mixed with and diluted by an unknown amount of the fluid given with the test meal. *Third*, it is not possible to determine the acidity of the total secretions entering the stomach; the only information obtained is the acidity

of the mixed gastric contents (meal plus secretions). *Fourth*, it is not possible to determine the relative amounts of acid and non-acid secretions entering the stomach during the test. *Fifth*, when the Ewald procedure is used, the curves are terminated at an arbitrary period (one hour). Since some subjects have a long, slowly developing curve while others have a short, rapidly developing curve, it is obvious that this method may fail to show the peak of the response in the former type of curve but may do so in the latter.

Histamine is widely used to overcome the low secretagogue content of the usual test meals but there is considerable evidence which suggests that histamine acts in an entirely different manner from the natural secretagogues in food (1, 2, 3). It has also been shown (4) that due to its unusual intensity the histamine

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stimulus is not controlled by the mechanism of acid inhibition. In this respect it is quantitatively or qualitatively different from the secretagogues normally present in food. It appears quite likely that histamine should be used only to determine whether or not the stomach is capable of secretory acid in response to a very powerful stimulus but not to study the normal secretory curve or the normal regulatory mechanisms.

The ground meat and water test meal which is often used in purely experimental studies presents certain grave analytical difficulties, due to the digestion of the meat, which usually lead to contradictory and grossly inaccurate results (5).

Wilhelmj, O'Brien and Hill (6, 7) developed a test meal consisting of a specially prepared two per cent solution of Liebig's meat extract containing 15 mgm. of phenol red per liter. When this test meal is used with the fractional method of gastric sampling, it eliminates most of the errors and deficiencies mentioned above. The preparation and use of this test meal have been described in detail in a previous communication (6) and will not be repeated here. It will suffice to state that when this test meal is employed, it is possible to determine the following factors on each gastric sample: (1) What proportion of the sample is fluid of the test meal still remaining in the stomach and what proportion is secretions which have entered the stomach. (2) The total secretions entering the stomach can be separated into the acid and non-acid secretions. (3) The acidity of the total secretions entering the stomach can be determined independently of the acidity of the mixed gastric contents. This test meal has been used in experimental work on dogs for several years and has proven highly satisfactory and it was decided to employ it in a study of the secretory curve in normal human subjects.

METHODS

All tests were performed in the morning without breakfast. A small Levine tube was introduced through the nose and firmly taped so that its position could not change during the test. The length of tube necessary to pass through the nose and pharynx and have the tip reach to about midway between the xiphoid and the umbilicus was measured and marked for each subject. Before introducing the tube the nose and pharynx were sprayed with a two per cent Pontocaine solution. The subject was instructed to spit out all saliva and this precaution was repeatedly emphasized during the test.

Three hundred cubic centimeters of the test meal to be used were introduced by gravity by pouring through the barrel of a 50 cc. syringe. After introduction, the lavage was repeatedly (10 to 15 times) withdrawn into the 50 cc. syringe and re-introduced. After repeated mixing the lavage was withdrawn as completely as possible. This preliminary lavage was very important in order to be certain that the stomach was empty before the test was started. It was not uncommon to find from 100 to 150 cc. of saliva, secretions or water in the fasting stomach, and if this had not been removed, the curves would have been greatly distorted.

After removal of the lavage 800 cc. of the test meal were introduced by gravity, by pouring through the syringe barrel, and the end of the tube firmly clamped. 800 cc. of meal was the amount used in all subjects. This amount is evidently well within the physiological limits since there was no complaint of fullness or distension. Samples (35 cc.) were removed every fifteen minutes until no further contents could be obtained. Samples were removed as long as any contents could be obtained regardless of the gross appearance of the samples, that is, re-

gardless of whether there appeared to be any test meal still present in the samples or not. Before removing each sample the gastric contents were very thoroughly mixed by repeated withdrawing and reintroduction with a 50 cc. syringe. This mixing process was kept up for 3 to 5 minutes before removing each sample in order to be certain that true aliquot samples were being obtained.

The methods of analysis and the calculations have been described in detail previously (6) but it is important to emphasize one point in connection with these studies on human subjects. Hollander (8, 9, 10, 11) has shown (in dogs) that the pure acid secretion, before admixture with mucus or other non-acid secretions, is secreted at a constant value of 0.170 normal and that this value is independent of the rate of acid secretion. It has also been shown that this value is not influenced by the degree of acidity of the gastric contents (4). Hydrochloric acid of this strength is isotonic with the blood. Evidence is accumulating (12, 13) showing that the pure acid secretion has the same value in the human subject and is also independent of the rate of secretion. Hence, in determining the amount of acid secretion in the gastric samples the cc. of tenth normal acid per 100 cc. of gastric contents were divided by 1.7 and the value expressed as the cc. of acid secretion. The total secretion in the gastric sample was determined from the decrease in the per cent of phenol red. The non-acid secretion is the difference between the total and acid secretion.

The amount of bile in each gastric sample was determined by the Pettenkofer ring test.

MATERIAL

The present report is based on 61 complete curves on 35 normal subjects. Several determinations (2 to 8) were performed on 15 subjects on whom a total of 41 curves were obtained. The majority of the subjects were sophomore medical students. None of the subjects included in this report had any abnormal gastro-intestinal symptoms.

RESULTS (Figs. 1 to 6)

One of the main questions which we wished to answer in this investigation was whether repeated tests on the same subject would show approximately the same type of curve each time or whether there would be wide variations. The curves in Figs. 1 to 6 show multiple curves on 12 subjects. These curves have been selected to show the extremes as well as the common types of curves encountered in all subjects.

One of the striking features of the experiments was that the maximum acidity of the gastric contents expressed as cc. of tenth normal acid per 100 cc. (clinical units) was in general much higher than the normal values usually given for total acid when the usual test meals are used. This is shown in column 2 of the table where it is seen that values of 100 or over were common in all groups. This is due at least in part to the greater secretagogue effect of the Liebig's extract meal.

(A) GENERAL DESCRIPTION OF THE CURVES

There are certain characteristics which are common to all curves and these will be described under the following headings:

1. *The Cubic Centimeters of Acid Secretion Per 100 cc. of Gastric Contents.* This is the acidity of the gastric contents expressed in terms of the pure acid secretion and it is represented by the black portion of the columns in the figures.

The acid secretion is usually low in the first sample after which there is a fairly rapid increase. Following this period of rapid increase the acid secretion may

follow one of three courses: (1) It may continue to rise but at a progressively slower rate; (2) The rise may cease entirely and the value remain practically constant until the stomach empties; (3) There may be a decrease as the stomach empties. A decrease occurred in 50 per cent of the curves.

II. *The Cubic Centimeters of Non-Acid Secretion Per 100 cc. of Gastric Contents.* The non-acid secretions include the mucus and mucoid secretions of the stomach itself and the regurgitated duodenal secretions as well as any saliva which may be accidentally swallowed. The non-acid secretions are represented by the white portion of the columns in the Figures.

The non-acid secretion is usually low in the first sample, after which there is an even and progressive increase until about the middle of the curve. During this period the rate of increase in the non-acid secretion is often relatively less than the rate of increase in the acid secretion. Near the end of the curve the increase in non-acid secretion becomes more rapid and relatively greater than the rate of increase in the acid secretion. This terminal increase is often very abrupt. The terminal increase in non-acid secretion is usually accompanied by the appearance of a positive Pettenkofer reaction in the gastric samples.

III. *The Acidity of the Total Secretions Entering the Stomach.* This is illustrated by the solid lines and dots in the Figures.

The acidity of the total secretions is dependent upon the relative amounts of acid and non-acid secretions present. If no non-acid secretions were present the acidity of the secretion would be that of the pure acid secretion (170 cc. of N/10 acid per 100 cc.), as the relative amount of non-acid secretion increases the acidity of the total secretions decreases.

The acidity of the total secretions may reach its highest value in the early part of the curve (first or second sample) or the peak may be postponed until near the middle of the curve. Following the peak, however, there is always a progressive decrease, which is often very abrupt, and which continues until emptying occurs. This behavior was characteristic of all normal curves. The maximal value reached is variable and depends entirely upon the relative amounts of acid and non-acid secretions present. In the early part of the curve the acid secretion may increase with great rapidity and there may be only very small amounts of non-acid secretion present so that the value may approximate 170 cc. of N/10 acid per 100 cc. in a single sample (experiments in lower third of Fig. 5). Following this value, however, there is always a rapid decrease.

(B) CLASSIFICATION OF CURVES

The general characteristics described above were found, with minor quantitative differences, in all 61 normal curves so that it was not possible to classify the curves on the basis of differences in the general contour.

The most striking difference encountered in these normal curves was the length, which varied from 1.0 to 2.25 hours. This permitted a rough classification into short, intermediate and long curves. Typical examples of each are shown in the Figures.

A detailed study of the 61 curves showed that there was no constant or significant difference in the maxi-

mal amounts of acid secretion or the acidity of the total secretions in long or short curves. This is summarized in the table which shows the *mean, maximal and minimal* figures for the highest values for the *uncorrected acidity of the gastric contents* (meal plus secretions) (column 2); the cc. of acid secretion (column 3); the cc. of non-acid secretion (column 4); the acidity of the total secretions entering the stomach (column 5) for curves of different lengths as well as for all 61 curves regardless of length. It is seen in this table that the highest values reached are not dependent upon the length of the curve. A long curve and a short curve may eventually reach the same maximal values and are thus related to one another as are a fast and a slow moving picture of the same event. From this it is evident that the amount of acid secretion per 100 cc. of gastric content is not necessarily related to or solely dependent upon the length of time that the meal remains in the stomach.

(C) A CONSIDERATION OF INDIVIDUAL CURVES

Fig. 1 shows a series of 8 experiments on the same subject made at irregular intervals over a period of four months. The first 7 curves are seen to be quite similar. The 8th curve was characterized by excessive duodenal regurgitation which began during the second

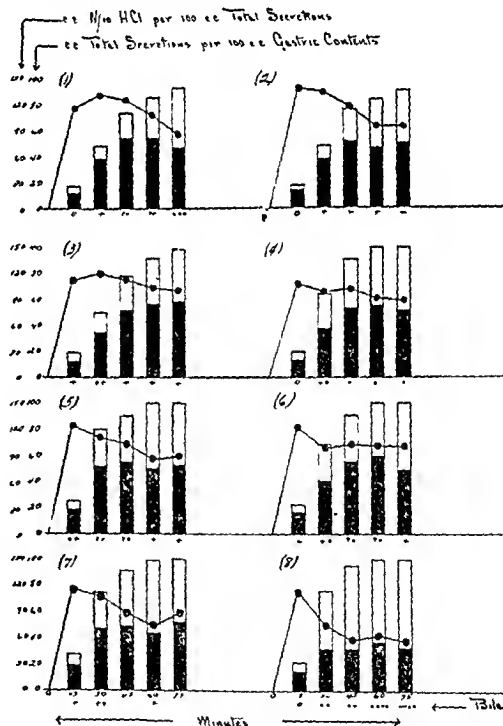


Fig. 1. 8 experiments performed on the same individual. Discussion in text. The height of the columns shows the cc. of total secretions entering the stomach per 100 cc. of gastric contents. The black portion represents the cc. of acid secretion and the white portion the cc. of non-acid secretion. The dots and solid lines show the acidity of the total secretions entering the stomach expressed as cc. of N/10 HCl per 100 cc. The zero and + marks represent the intensity of the Pettenkofer reaction on the basis of 1 to 4. Samples collected every 15 minutes. These insignia are the same in all figures.

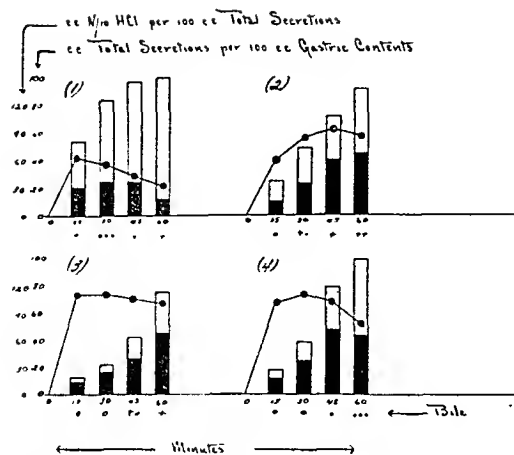


Fig. 2. 4 experiments on the same individual. Discussion in text.

period and continued throughout the experiment. There was no nausea. It was demonstrated that the tip of the tube was in the mid-part of the stomach and had not slipped into the duodenum. It is seen that the most striking effect of the excessive duodenal regurgitation was the lowering of the acidity of the total secretions entering the stomach, the lowering of the acidity of the contents (cc. of acid secretion) was less striking.

Fig. 2 shows four experiments on the same subject. Experiments 2, 3, and 4 are in good agreement. In Experiment 1 the subject became nauseated during the first 15 minute period and the nausea continued throughout the experiment. The result of the nausea was a lowering of the acid secretion and an increase in the non-acid secretion. This same effect of nausea has been noted on several occasions.

Fig. 3 shows four experiments on a subject with the longest curve encountered (2 to 2.25 hours). The four curves which were obtained at irregular intervals over a period of several months are in reasonably good agreement. This subject is a technical laboratory assistant and has been observed over a period of nearly one year, and there is nothing to suggest the slightest abnormality in his gastro-intestinal function; hence, this long type of curve must be considered as entirely normal. However, as shown in the table, only 3

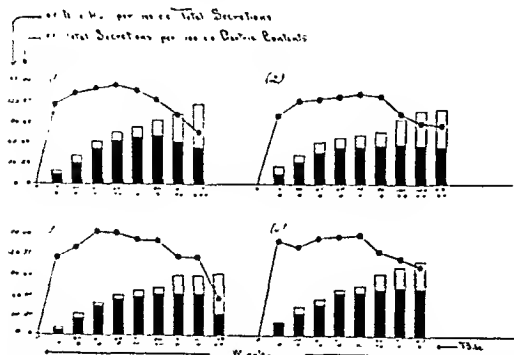


Fig. 3. 4 experiments on the same individual. Discussion in text.

subjects out of the 35 had curves of this extreme length.

Fig. 4 (upper third) shows four experiments on the same subject which are in good agreement. The middle third shows two experiments on the same subject in which the second experiment shows a definitely higher acid secretion than the first. A possible explanation of this finding will be mentioned later. In the lower third are shown two experiments on the same subject which are in fair agreement.

Fig. 5 shows two experiments on each of three subjects. The subjects shown in the upper and middle thirds show good agreement between the duplicate curves and no special comment is necessary. The curves on the subject shown in the lower third are

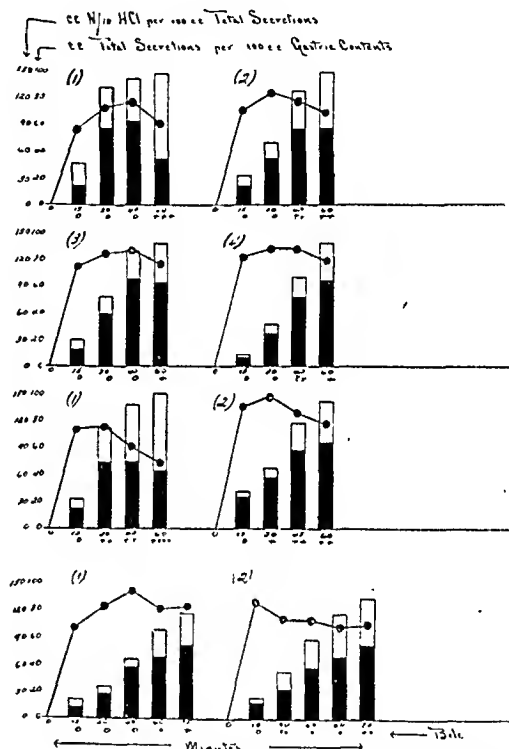


Fig. 4. Upper third. 4 experiments on the same individual. Middle and lower thirds. 2 experiments on each of two individuals. Discussion in text.

interesting. In both experiments the acid secretion increases rapidly during the early part of the curve and during this period the non-acid secretion is very small in amount. In both curves this results in one or two samples in which almost no non-acid secretion is present and in which the acidity of the total secretions reaches a value approximating the acidity of the pure acid secretion (170 cc. of tenth normal acid per 100 cc.). Following this, however, the non-acid secretion begins to increase relatively more rapidly than the acid secretion with a resulting rapid fall in the acidity of the total secretions.

Fig. 6 (upper third) shows two experiments on the same subject in which the emptying time is decidedly different (1.5 hours in experiment (1) and 1.0 hour

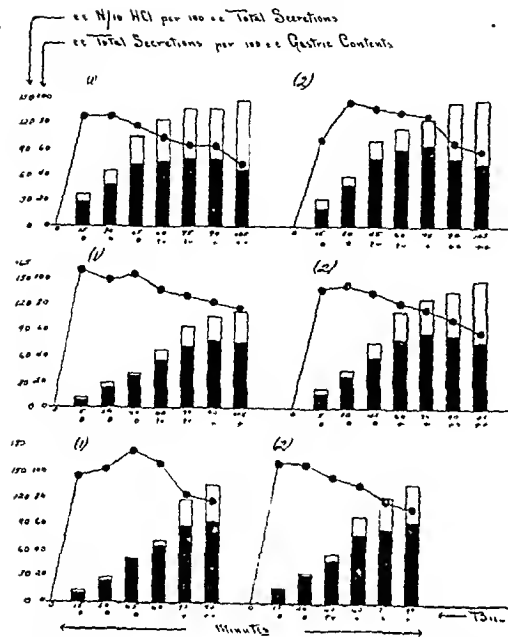


Fig. 5. Upper, middle and lower thirds show two experiments on each of three individuals. Discussion in text.

in experiment (2). It is interesting to note that in spite of the difference in the lengths of the curves the maximal amount of acid secretion present as well as the acidity of the total secretions is not materially different. It simply requires longer for the maximal value to develop in the long curve than in the short curve. A somewhat similar but less marked example is shown in the lower third of the figure. In the subject shown in the *middle third* of the figure the second curve is rather definitely lower than the first.

DISCUSSION

There is considerable variation in the curves of different normal individuals but when multiple curves are obtained on the same individual the agreement is usually quite satisfactory. The number of samples obtained from the same subject usually does not vary by more than one fifteen minute sample. (The subject shown in the upper third of Fig. 6 shows the greatest variation encountered in this series). The cubic centimeters of acid secretion per 100 cc. of gastric contents is usually quite constant in the same individual. The amount of non-acid secretion which regurgitates from the duodenum into the stomach is one of the most variable factors encountered when multiple curves are obtained on the same individual, and this in turn causes corresponding variations in the acidity of the total secretions entering the stomach.

The increase in the non-acid secretion and the fall in the acidity of the total secretions entering the stomach, which become most pronounced near the end of the curve, are primarily due to the regurgitation of duodenal secretions into the stomach. The acidity of the gastric contents is to some extent independent of duodenal regurgitation and is controlled primarily by the mechanism of "acid inhibition" which operates to decrease the amount of acid secreted as the acidity of

the gastric contents rises. The relative roles played by duodenal regurgitation and acid inhibition in the human subject will be demonstrated in a future paper.

During the course of these studies an interesting observation was made regarding the effect of mild acute alcoholism on the gastric secretory curve. In four instances the subjects stated that they were suffering from a mild "morning after" complex. Three of the subjects had had one or more curves obtained under normal conditions. The "morning after" curves varied definitely from the previous normals, the most striking differences being an increase in the amount of acid secretion and a decrease in the amount of non-acid secretion with a consequent elevation of the acidity of the total secretions. There was no nausea while the experiments were in progress; otherwise there would probably have been a marked increase in non-acid secretions.

In attempting to establish the maximal and minimal values for the normal gastric secretory curve one is confronted by several unknown factors. For example, will the values obtained on a group of normal sophomore medical students be the same as the normal values in the social group which contributes the free clinic patients in any large urban center? Aside from the age factor, the medical student is living a more or less harried life of stress and strain which is entirely different from the life of the average free clinic patient who comes from a social stratum which has largely east aside individual responsibility and expects the government to support and protect him and his offspring. Unpublished experiments performed a few years ago indicate that the normal values in the free clinic group may be considerably lower than in a

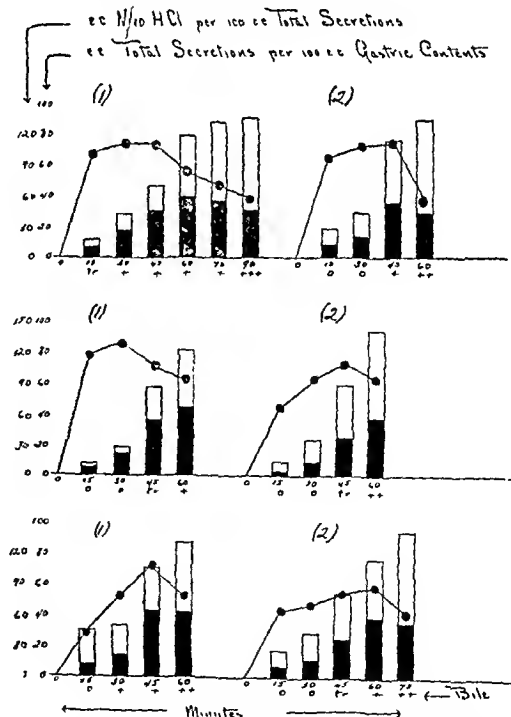


Fig. 6. Upper, middle and lower thirds show two experiments on each of three individuals. Discussion in text.

(1) Length of Curve	(2) Uncorrected Acidity of Contents—cc. N/10 HCl per 100 cc.	(3) cc. of Acid Secretion Per 100 cc. of Gastric Contents	(4) cc. Non-Acid Secretion Per 100 cc. of Gastric Contents	(5) Acidity of Total Secretion cc. N/10 HCl per 100 cc.	(6) Number of Curves	(7) Number of Subjects
1.0 Hours	mean — 84 max. — 111 min. — 44	mean — 48 max. — 65 min. — 24	mean — 48 max. — 88 min. — 28	mean — 103 max. — 146 min. — 63	15	7
1.25 Hours	mean — 89 max. — 112 min. — 62	mean — 51 max. — 64 min. — 35	mean — 50 max. — 75 min. — 22	mean — 124 max. — 175 min. — 87	18	10
1.50 Hours	mean — 98 max. — 109 min. — 86	mean — 56 max. — 63 min. — 39	mean — 41 max. — 60 min. — 29	mean — 143 max. — 171 min. — 111	9	7
1.75 Hours	mean — 93 max. — 108 min. — 69	mean — 53 max. — 60 min. — 35	mean — 45 max. — 54 min. — 24	mean — 126 max. — 167 min. — 80	12	8
2.0 Hours and 2.25 Hours	mean — 90 max. — 107 min. — 75	mean — 49 max. — 60 min. — 39	mean — 37 max. — 52 min. — 20	mean — 145 max. — 155 min. — 131	7	3
All Curves	mean — 90 max. — 112 min. — 44	mean — 51 max. — 65 min. — 24	mean — 44 max. — 88 min. — 20	mean — 128 max. — 175 min. — 63	61	35

An analysis of the maximal values obtained in curves of different lengths. Column 1—Lengths of the curves. Column 2—Gives the mean, maximum and minimum values of the maximal acidity of the gastric contents (meal plus secretions) without correction for the titratable acidity of the test meal used. Expressed as cc. N/10 HCl per 100 cc. (clinical units). Column 3—Gives the mean, maximum and minimum values for the greatest amount of acid secretion per 100 cc. of gastric contents. Column 4—Gives the mean, maximum and minimum values for the greatest amount of non-acid secretion per 100 cc. of gastric contents. Column 5—Gives the mean, maximum and minimum values for the highest acidity of the total secretions entering the stomach. Column 6—Number of curves in each group. Column 7—Number of subjects in each group. In the lower part of the table the values are shown for all curves regardless of length.

group of medical students. Hence, it is quite possible that the normal curves published in this paper are normal only for the type and class of individuals studied. The high incidence of duodenal ulcer in professional men and business executives indicates that this concept may be more than idle fancy.

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DISCUSSION

DR. FRANKLIN HOLLANDER (New York): Mr. Chairman: The first attempt at the use of a dilution indicator, so far as I know, was made back in 1896. During the forty years which have intervened between then and now, nobody has devoted himself as assiduously to the investigation of the dilution indicator technique as has Dr. Wilhelms, and I think he is to be very strongly commended for his persistence.

Some of the conclusions which he has arrived at by the use of this technique, he has presented today. These conclusions are extremely important, but from some of the work which we have been doing in our own laboratory during the last year and a half, we have reason to question the validity of some of these conclusions. I should like to show you some of the evidence on which I base this statement.

About a year ago Doctors Penner and Bnndes, working in our laboratory, started some work with phenol red as a dilution indicator. These studies on humans, in which an alcohol test-meal was used, were followed through much as are Dr. Wilhelms's experiments, but the results were

very surprising to us and not entirely explicable at that time. We therefore decided to discontinue the study with human subjects and to take up the work on dogs, which would permit our going into more varied and extensive work than we could with patients.

(Slide) We repeated the alcohol test meals with dogs and got results which are typified by the graph of this particular experiment. The broken lines represent chloride and acidity as observed on each specimen directly. When these results are corrected for dilution by the test-meal, we get the curves represented by the unbroken lines.

Let me limit my discussion to the chloride concentration, to simplify matters. You observe that the chloride concentration in these experiments, on correction, rose to values as high as 350 millimols per liter, which corresponds to a value of well over 1200 milligrams per hundred cc. (600 milligrams, or 165 millimols, corresponds to the isosmotic value). In fact, practically all the values in this experiment were above 165. Since every one of our experiments gave similar results we were forced to conclude either that an extremely hypertonic solution, of which we have hitherto been ignorant, is formed somewhere in the gastro-intestinal tract, or else that a considerable amount of water and alcohol was absorbed in the course of these experiments. Such absorption would introduce a considerable error in our estimations of the chloride concentration of the gastric secretion.

(Slide) We therefore repeated these experiments using a test-meal of water and phenol red, and our chloride values are almost all above 165mM, as with the alcohol test-meals.

(Slide) We then went back to Dr. Wilhelms's papers and studied them more carefully than we had ever done, and we found two whole sets of experiments in which he obtained similar results. The graphs on this slide are made up from one of his experiments. You will observe that here also the chloride values rise persistently above 165mM, thus forcing us to the conclusion that water absorption was occurring in all of these experiments with a hypotonic test-meal. In order to verify this conclusion, (slide) we next performed experiments with isotonic test-meals, containing sodium chloride at a concentration of

165 millimols. In such experiments the calculated chloride concentrations never rose above a value of 175mM, as is illustrated by this chart. Since the use of an isotonic test-meal probably minimizes the absorption of water, and since it definitely eliminates the abnormally high chloride values, we feel that these experiments are also indicative of a connection between the two phenomena.

Consequently, if it be true that the small amounts of water absorption which are taking place in the stomach give us such erroneous results, it must be concluded that any generalizations which are drawn from experiments of this kind are open to serious errors and therefore to grave suspicion. The results of these investigations will be published shortly in detail.

DR. CHARLES M. WILHELMJ (Omaha): In reply to the comments upon Dr. Sachs's statement that we have found considerable variation in different normal subjects, that is quite true, and it has been rather difficult for us to say just what constitutes a normal curve. We are attempting at the present time to establish that, but one thing which has been very hopeful is that we find when multiple determinations are done upon the same human subjects, they agree surprisingly well.

It may be possible later on to delineate the limits of the normal curve. We have found in general that the student group which we have reported on are rather higher than people who make up the clinic group, those who have minor ailments and no gastro-intestinal complaints.

As to the point made by Dr. Hollander, regarding water absorption, we, too, of course, observed this a long while ago. Up to the present time I have studied somewhat over a hundred dogs, using this test meal and we have done probably in the neighborhood of eight or nine hundred determinations, and this mechanism of water absorption is rather uncommon. Some animals show it all the time

while in others it may never be seen. Up to the present time we have studied only one human subject who showed this phenomenon.

I do not agree that that is to be looked upon as an error. I believe that small amounts of water are always being absorbed from the stomach; that it is a normal physiological process. Ordinarily, however, when this method is used, absorption of water is masked when sufficient quantities of non-acid secretions enter the stomach. I am inclined to look upon it as a physiological mechanism and not as an error.

I have quite recently classified this as one type of hyper-acidity in which the acidity of the total secretions entering the stomach is elevated way above the normal value due to water absorption. If you were not using the phenol red method, you would never detect that, never know it occurred, so I am inclined to put an entirely different interpretation upon it than Dr. Hollander did.

DR. ADOLPH SACHS (Omaha): The Liebig's extract meal is at present a research method and of more value in selected clinical cases. We hope to modify it for general clinical use. It gives valuable information on acid inhibition and duodenal regurgitation that no other meal gives. It has definite value in selected cases and may indicate the ulcer groups. It tells us of the hyper- and hypo-acid groups.

Secretory curves are variable in different individuals but are surprisingly constant in the same individual. There is some difficulty in establishing normal values. Our student group ran high but this is our potential ulcer group of highly organized individuals. Our colored group ran much lower and also our outpatient clinic group.

I feel that this meal is going to prove of even greater value as our methods are improved and simplified.

The Absorption and Dilution of Glucose Solutions in the Human Stomach and Duodenum*

By

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WE had the opportunity several years ago, to study, for a short time, a patient who, in good health at the time, had been operated several years before for a low intestinal obstruction. At operation so much intestinal distention must have been present that the surgeon performed a high jejunostomy instead of an intended ileostomy. We fitted a small rectal tube with a balloon for retention in the gut, and were thus able to collect the contents of the proximal portion of the jejunum. By intubating the upper duodenum in the usual manner and administering glucose meals orally, we were able to study simultaneously the behavior of such solutions at the upper duodenum and jejunum. Based on these observations, in a discussion of a paper by Abbott, Karr and Miller (1) in May, 1937, before

this Society, we (2) expressed the opinion that the duodenum and upper jejunum are far more important as dilution sources for hypertonic glucose than is the stomach. Table A illustrates the result that prompted such a conclusion. It was seen that in a 15-minute period after the ingestion of 250 cc. of a 36.5% glucose, the concentration in the stomach was decreased to 25.6% and that the volume was increased from 250 cc. to 285 cc. The fact that in the first 15-minute period the range of glucose concentration lay between 25.6% and 36.5% points to this as the probable peak of gastric volume. Our previous experiments have indicated that gastric emptying in this range is very slow (3). That this was true can be deduced by an estimate of the glucose recovered through the fistula. Assuming that the rate of absorption from the duodenum and upper jejunum remains fairly constant, the rapid increase in total glucose recovered

*From the Medical Research Laboratory, Samuel S. Fels Fund and the Gastro-Intestinal Division, Medical Service I, Mt. Sinai Hospital. Read at the Annual 1939 Session of the American Gastro-Enterological Association at Atlantic City.

in the first three 15-minute periods can be taken as a measure of the inverse relation between gastric glucose concentration and gastric emptying. The glucose recovered at the fistula during these periods was 6.9 gms.; 16.2 gms. and 26.7 gms. respectively.

Since we were unable to study the problem in this patient in reliable quantitative fashion, and since our

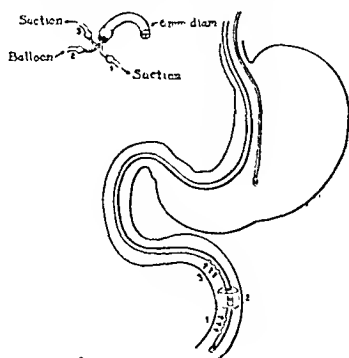


Fig. 1

modern Alexis was as uncooperative as his famous predecessor, we abandoned further studies on him.

Abbott, Karr and Miller (1) have recommended the use of a three-lumen tube furnished with two balloons for intestinal absorption experiments. They believe that in studying absorption in segments of the small intestine isolated between two balloons, an objective measurement of the process per se can be obtained. Groen (4) in her studies of intestinal absorption employed the double lumen tube. She used one lumen for the tip and balloon, and perforations in the second lumen just above the balloon for the intestinal instillation and subsequent extraction of the test substances.

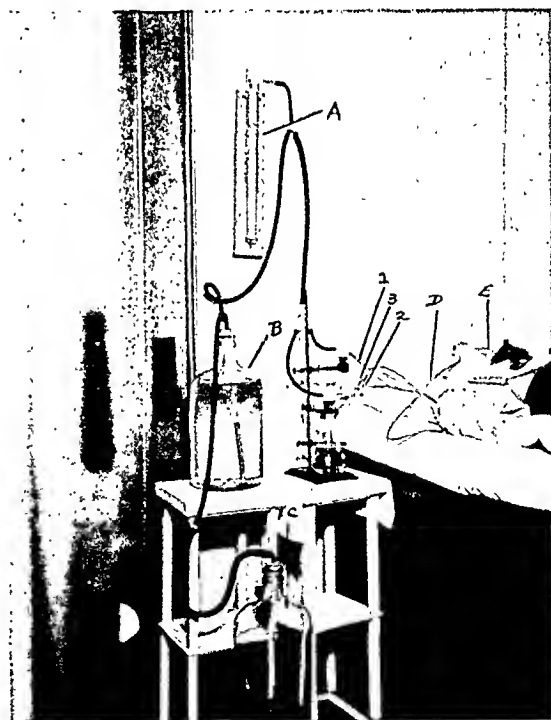
By modifying the three lumen tube to meet the needs of our experiment, we have been able to study the absorption and dilution of sugar solutions in the stomach alone and in combination with varying lengths of small intestine.

After numerous preliminary experiments, we settled upon the following tube arrangement: To lumen 1 of the three-lumen Miller-Abbott tube we attached a perforated bucket. In the same lumen for a distance of four inches above the bucket we placed three or four perforations. Lumen 2 carries the perforations for the balloon. (See Fig. 1). Above the balloon, in the wall of the third lumen, are three perforations an inch apart. The compartments in the three-lumen tube are not of equal size. We selected the largest for the third lumen because through this the intestinal contents were to be recovered. To lumina 1 and 3 constant suction equal to about 70 cms. of water was applied throughout the experiments. A mercury manometer was inserted in the circuit to be certain that our suction was constant. The advisability of collecting the material beyond the balloon became evident in preliminary experiments and will be discussed later. (See Photograph)

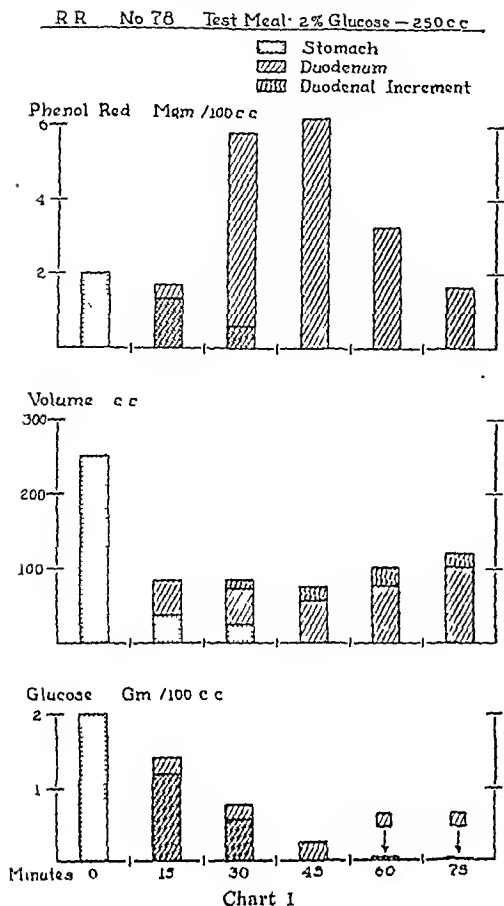
In order to study absorption of the glucose in the various segments, as well as to have some easily detectable indicator to discover any leakage beyond the occluding balloon, we added phenol red to the test meal. Penner, Hollander and Saltzman (5) have shown

that this dye is not adsorbed or absorbed by the human stomach. We (6) have confirmed their report. While our results indicate that there is a small amount of absorption or adsorption of this dye by the duodenum, it has not interfered with its usefulness in our present experiments. It has also served as an excellent indicator of the rapid shift that can be made by the duodenum from water excretion to water absorption. This dye was added to the test solutions in concentration of 2 mgms. per 100 cc.

We used a different approach to study the behavior of various intestinal segments. Since we do not know how long intestinal contents are normally retained in any one segment, we considered it more physiological to introduce the test substance at the proximal end of the intestinal segment to be studied, allow it to progress unhampered through the intestinal segment, and to collect the material from the distal end of that segment. This was accomplished by the use of a four-lumen tube. These tubes were made from our specifications by The George P. Pilling and Son Company, Philadelphia. By using an 18 F. (outside diameter 6 mm.) instead of the 16 F. (outside diameter 5-1/3 mm.) of which the three-lumen Miller-Abbott tube is constructed, we increased the outside diameter only 2/3 mm. and were able thereby to have the additional compartment. Three lumina are identical with those described for the three-lumen tube. The wall of the fourth lumen is perforated above the balloon at a distance equal to the length of intestine to be studied. A small metal plug was inserted just distal to the last perforation in the fourth lumen. This plug serves two



1. Suction from tip of three-lumen tube. 2. To the balloon. 3. Suction from above balloon. A. Mercury Manometer. B. and C. Bottles providing suction. D. Three-lumen tube to duodenum. E. Single-lumen tube to stomach.



purposes: it facilitates locating the perforations in this lumen by X-ray and stops the lumen distal to the perforation, so preventing any loss of the test fluid in the blind end. With the tube in place, suction was applied through the perforations above and below the balloon while the test substance was instilled at the desired rate through the perforations in the fourth lumen. The test material traversed the segment of bowel isolated between the perforations through which it was instilled and those above the balloon where it was withdrawn by the constant suction applied to this lumen. In the flask receiving the material from lumen 1, a small amount of calcium oxide is placed. This changes any phenol red in this material to the alkaline (red) form, and thus acts as an indicator of leakage beyond the balloon.

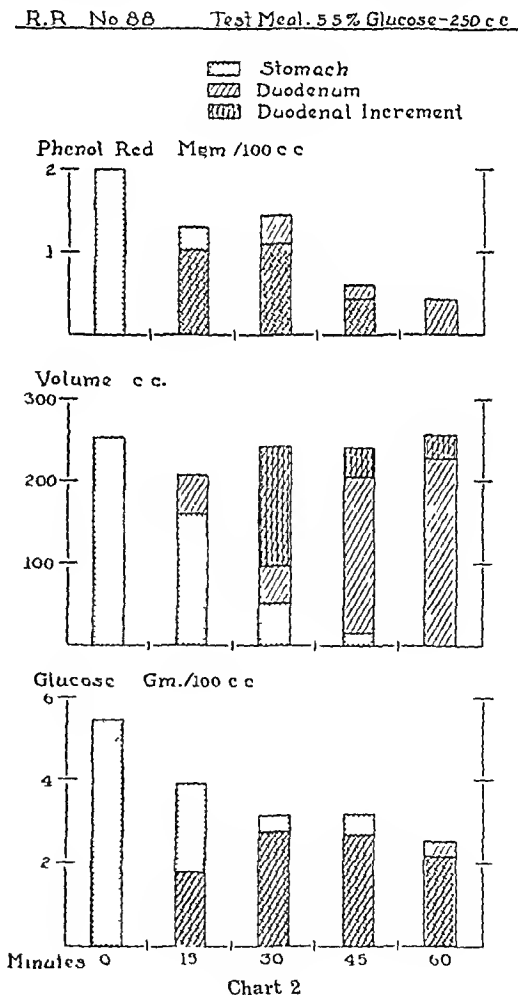
We are limiting ourselves here to the behavior of various concentrations of glucose in the stomach alone, in the stomach and duodenum when instilled into the stomach, and in the duodenum alone when instilled directly into its proximal end. When the whole gastro-duodenal segment was studied, we placed a second, single-lumen tube in the stomach through which we made our gastric instillations and extractions.

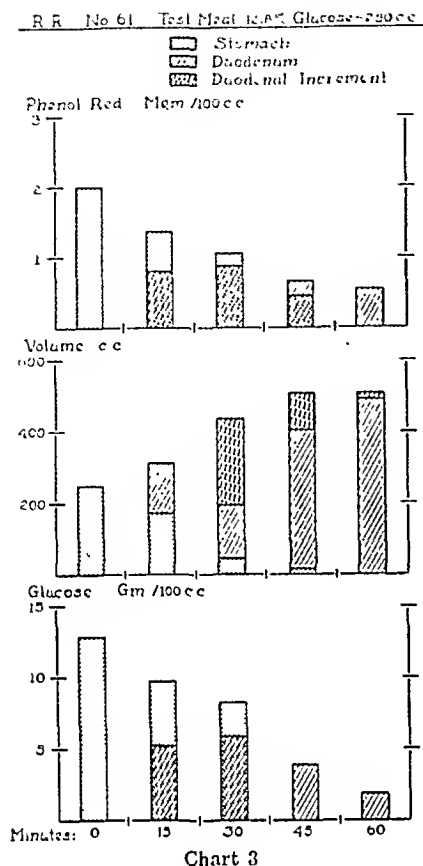
EXPERIMENTAL METHOD

Patients with no organic disease of the gastro-intestinal tract were selected. In studying the gastro-duodenal segment, the patient, after an overnight fast, was intu-

bated with two tubes; one, the three-lumen tube as described above; and the other, the usual single-lumen tube employed for gastric analysis. The duodenum was intubated with the triple-lumen tube by the usual technique. Duodenal intubation was determined by fluoroscopic examination. When the tip of the tube was in the second portion of the duodenum, the balloon through lumen 2 (see Fig. 1) was inflated with 15 cc. of air. This permitted the tip to be carried along rapidly to the desired location in the intestine by peristalsis. When the balloon reached this point, it was further slowly inflated with 30-35 cc. of air, the inflation being kept just below that amount which caused abdominal pain. In these studies, the attempt was made to advance the balloon so that its proximal edge was just beyond the duodenal jejunal junction. The position was determined fluoroscopically, and the tube then made taut by traction at the mouth, to make certain no slack remained in the stomach. Then the tube was fixed firmly at the lips with several pieces of adhesive tape. If these precautions are not taken, there is likely to be gastric slack which may cause the balloon to be carried too far during the experiment.

Studies were done using hypertonic solutions of glucose about 40% and 13%. The latter was chosen because Magee and Reid (7) reported 13.5% glucose the best concentration for intestinal absorption. Studies were also done with solution around isotonicity (5.4%) and hypotonic (about 2%) glucose solutions. In the study of the



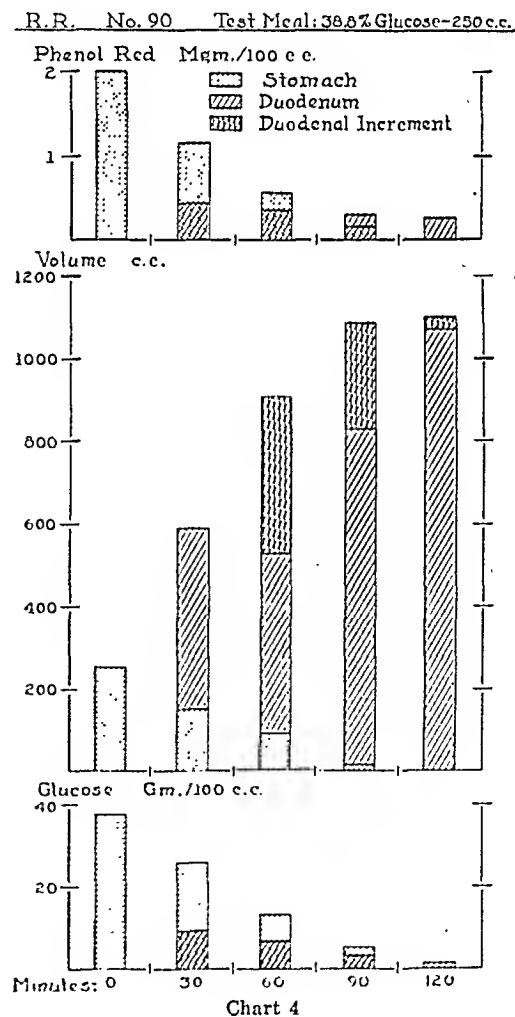


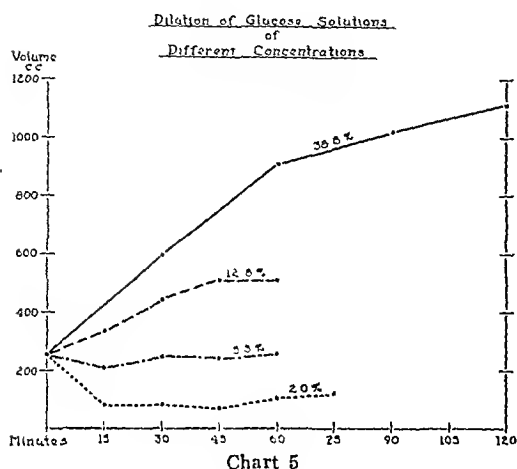
complete gastro-duodenal segment, with both tubes in place, suction was applied to lumina 1 and 3 for a fifteen minute period in order to collect the fasting sample. At the end of this period, the stomach was emptied through the gastric tube and the specimen retained for analysis. The gastric tube was then slowly withdrawn to the 55 cm. mark and reintroduced for two or three cms. so that the tip was just beyond the cardia. The test meal (250 cc.) containing the glucose and phenol red was then introduced into the stomach. We used this method to introduce the meal so that the patient would be spared any unpleasantness, especially from the 40% glucose solutions. By bringing the tip of the tube near the cardia, the meal had a good opportunity to spread over the entire gastric surface and so simulate natural ingestion. As the meal was introduced into the stomach, fresh flasks were attached to the lumina through which we were applying suction. At 15 or 30 minute intervals, from the beginning of the instillation of the meal, depending on its concentration, the stomach was emptied as completely and as quickly as possible; the recovered volume was measured and mixed; 10 cc. retained for analysis; and the remainder returned immediately to the stomach. The recovery from the duodenum through lumen 3 was fractionated into similar 15 or 30 minute samples. This fractionation continued until the stomach was empty, while collection from the duodenum proceeded for a half-hour after the stomach was empty. The gastro-duodenal segment was then lavaged by successively administering 3-250 cc. portions of normal saline orally at half-hour intervals, while continuous suction was applied as before. The first lavage fluid usually appeared at the suction point within 5 minutes. This was recognized by a rapid flow of fluid through lumen 3

in contrast to a period of practically no flow. The lavages were collected separately and collection continued for 30 minutes after the ingestion of the last lavage. The material from lumen 1 was collected in one receptacle until the beginning of the lavages. If any phenol red was detected in this material, the experiment was discarded.

On another day, after collecting the fasting gastric and duodenal specimens as previously described, the glucose meal was introduced directly into the upper duodenum through the proper compartment of the four-lumen tube (see Fig 2). The meal was instilled at the rate of approximately 15 cc. every 5 minutes, with a Murphy drip bulb used intermittently to regulate the flow. In these studies, we used the 2%, 5.4%, 13% and 23% glucose solutions. The collection by suction from the lower end of the duodenum was fractionated somewhat differently from that described above. The first fifteen-minute specimen following the introduction of the meal was collected separately. With stop-watch control two half-hour specimens were collected, instillation of the test meal continuing throughout these periods. After this, all the duodenal material was collected in one specimen, the collection continuing for thirty minutes after completion of the duodenal instillation of the meal. Lavages were then carried out as described. All fluids were introduced into the duodenum at or near body temperature.

On other days, the absorption and dilution by the





stomach alone of glucose solutions similar to those used in the preceding experiments were studied. The method here employed was that used previously (8). After an overnight fast, the stomach was intubated with two duodenal tubes. One was passed to the duodenum in the usual manner, while the second remained in the stomach. Through the duodenal tube olive oil was instilled at the rate of 50 to 60 drops per minute. This usually produced very rapid complete pyloric closure. The stomach was completely emptied in all positions. About 5 minutes after the duodenal instillation of the oil was started the test solution of glucose and phenol red was introduced by gravity through the gastric tubes and allowed to remain for 30 minutes. The stomach was then emptied in all positions through the gastric tube and lavaged with three portions of 250 cc. of distilled water around body temperature, which was administered and removed through the gastric tube. The volume of each sample was measured and analysis done for phenol red, glucose and chloride. Phenol red was determined by the method of Hollander (9) plus the additions suggested by Wilhelmj (10) and ourselves (6).

We found that alkalization with calcium oxide was unnecessary for the determination of phenol red in the duodenal specimens, since the calcium oxide combined with the bile acids without effecting much change in pH. We found that the pH of the intestinal contents as collected from the lower end of the duodenum ranged between pH 6.5 and 7.8 and that we could obtain complete precipitation of the bile material without preliminary neutralization.

Glucose was determined as follows:

A preliminary approximation of the concentration in each sample was made by the usual method with Benedict's solution. On the basis of these values, the samples were diluted to contain approximately 100 mgms. per 100 cc. This diluted solution was precipitated with sodium tungstate and sulphuric acid and the filtrate analysed by the Folin Wu method.

Absorption or excretion of water was gauged by the change in concentration of the phenol red in the duodenal contents as compared with that at which the dye reached the duodenum.

Total chloride was determined by the Wilson and Ball (11) method.

ANALYSIS OF DATA AND DISCUSSION

1. Absorption of Glucose by Stomach and Duodenum Acting as a Unit.

That the duodenum plays an important part in the absorption of glucose is rather widely accepted. Omi (13) and Frey (14), in the dog, and more recently,

Abbott, Karr and Miller (1), in human subjects, support such a concept. Nagano (12) from his studies in vella-fistula dogs concluded that sugar was resorbed relatively more rapidly in the upper portion of the intestine than water. On the other hand, King, Arnold and Church (15) found in dogs that glucose was absorbed more rapidly in the jejunum than in the duodenum and ileum. Our results indicate that the duodenal function is remarkable in that it can shift rapidly from an actively absorbing mechanism to just as actively a secreting one. The question of absorption or non-absorption of glucose and water by the duodenum is, we believe, dependent purely upon the concentration of glucose instilled into the stomach. We found in the case illustrated (Charts 1 to 4) that when 250 cc. of a 2% glucose solution was instilled into the stomach, 4.14 gms. were absorbed by the time the lower duodenum was reached. With an isotonic solution, 7.57 gms. were absorbed; with 12.8% solution, 4.1 gms.; and with a 38.8% solution, the absorption was 17.4 gms. These represent respectively 82.8%, 54.3%, 12.8% and 17.9% of the total amount of glucose instilled.

Using the stomach and duodenum as a complete segment, we saw no constant rate of absorption per unit time independent of concentration or total glucose as described by Cori (16) for the whole intestinal tract for the rat, or Trimble, Carey and Maddock (17)

Osmotic Pressure of Lower Duodenal Contents Following Ingestion of Various Concentrations of Glucose

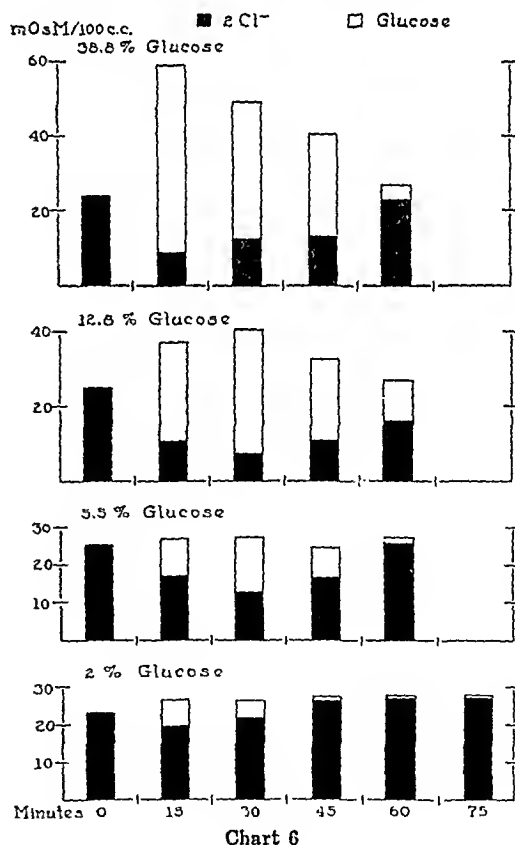


TABLE V

Osmotic Pressure of Gastric Samples

Concentration of Test Meal		Time			
		Glucose		2Cl ⁻ mOsm 100 cc	Total mOsm 100 cc
		gm 100 cc	mOsm 100 cc		
2.0%	Meal	2.0	11.10	0	11.10
	Fast	0	0	12.42	12.42
	15	1.36	7.54	7.96	15.50
	30	0.16	0.83	14.98	15.81
	45	0.16	0.83	14.98	15.81
5.5%	Meal	5.55	30.42	0	30.42
	Fast	0	0	14.00	14.00
	15	3.88	21.53	4.56	26.09
	30	3.16	17.53	7.16	24.69
	45	1.16	6.43	16.04	22.47

centrations. With the 12.8% glucose somewhat over twice an isotonic solution, twice the volume of instilled meal was recovered. Although the volume after 38.8% glucose meal was much greater (1103 cc.) about 4.5 times the instilled volume—it is obvious that no linear relationship between concentration and volume recovery exists. For such a linear relationship to be present we would have had to recover approximately 1700 cc. after the 38.8% glucose meal. We could not show any square root relationship of concentration either to absorption or to volume recovered, as reported by Arrhenius (22).

TABLE VI

R.R. No. 62

Test Meal 2.8% Glucose—250 cc into Duodenum

Time	Volume		Total Vol		Glucose		Cl ⁻ mOsm 100 cc	Total mOsm 100 cc	Phenol Red	
	In	Out	In	Out	gm 100 cc	mOsm 100 cc			mm 100 cc	mm 100 cc
Fast	0	4	4	0	0.25	0.25	0.25	10.62	21.64	21.00
15	15	4	45	4	0.23	0.14	1.27	11.54	24.35	29.5
45	50	6	135	10	0.35	0.35	1.84	12.85	27.70	30.3
75	90	7	223	31	0.15	0.25	0.25	13.10	26.20	30.3
90	25	5	250	36	0.16	0.16	0.64		1.63	2.61
L ₁		160							0.15	0.36
L ₂		235								
L ₃		242								

	Glucose	Phenol Red	Volume
Given	7.16 gm	5.00 mm	250 cc
Recovered	0.27 gm (3.9%)	4.11 mm	36 cc
Absorbed	6.91 gm (96.1%)		214 cc

OSMOTIC PRESSURE IN THE LOWER DUODENUM AFTER VARIOUS CONCENTRATIONS OF GLUCOSE SOLUTIONS PLACED IN STOMACH

Karr and Abbott (23) have shown that the only significant osmotically active solutes in the fasting intestinal contents are the chloride and bicarbonate salts. They presented data showing the close approximation between the sum of the chloride and bicarbonate ions and the total base. On this basis they produced a sufficient approximation of the osmotic pressure of fasting intestinal contents by multiplying the

sum of the chloride and bicarbonate ions, expressed as milli-equivalents per liter, by two, to obtain the milliosmoles. When glucose is present the osmotic pressure may be expressed as 2 Cl⁻ plus 2 HC03⁻ plus glucose all in milli-equivalents per liter. For our calculations we have not determined bicarbonate, and believe, as Groen does, that for practical purposes this may be ignored. Even if we take the average of the duodenal bicarbonate figures reported by Abbott, Karr and Miller (1), it would add 2.1 milliosmoles per 100 cc. to our figures and would not materially alter our present findings.

Chart 6 shows the osmotic pressure calculated for the patient illustrated, on the basis of 2 Cl⁻ plus glucose. The fasting duodenal contents were always very slightly hypotonic (23-25 milliosmoles per 100 cc.), even if the 2.1 milliosmoles per 100 cc. of bi-

TABLE VII

R.R. No. 98

Test Meal 4.4% Glucose—250 cc into Duodenum

Time	Volume		Total Vol		Glucose		Cl ⁻ mOsm 100 cc	Total mOsm 100 cc	Phenol Red	
	In	Out	In	Out	gm 100 cc	mOsm 100 cc			mm 100 cc	mm 100 cc
Fast	0	5	5	0	0.16	0.02	0.11	15.00	30.00	0.04
15	45	12	45	12	0.73	0.01	0.05	11.83	23.71	1.33
45	90	14	135	26	0.10	0.03	0.17	13.22	26.71	2.90
75	90	26	225	54	0.17	0.05	0.28	14.02	28.32	4.60
90	25	28	250	62	0.01				0.98	2.10
L ₁		218			0.01				0.01	0.01
L ₂		150			0.01					

	Glucose	Phenol Red	Volume
Given	11.00 gm	5.00 mm	250 cc
Recovered	0.11 gm (1.0%)	4.41 mm	62 cc
Absorbed	10.89 gm (99.0%)		188 cc

carbonate were added. Following instillation of a 2% glucose solution into the stomach there was a close approximation to isotonicity, the concentration of chloride being slightly depressed early with the replacement by glucose. The same was true when the isotonic glucose was instilled, but this time there was a greater temporary replacement of chloride by glucose in the duodenum. Following instillations of 12.8% and 38.8% glucose solutions, the osmotic pressure in the lower duodenum remained above isotonicity. The reciprocal shift of chloride and glucose concentration is clearly illustrated—findings similarly described by Abbott, Karr and Miller (1). It is interesting to note that al-

TABLE VIII

R.R. No. 96

Test Meal 14.4% Glucose—250 cc into Duodenum

Time	Volume		Total Vol		Glucose		Cl ⁻ mOsm 100 cc	Total mOsm 100 cc	Phenol Red	
	In	Out	In	Out	gm 100 cc	mOsm 100 cc			mm 100 cc	mm 100 cc
Fast	0	2	2	0	0.12	0.01	0.04	9.36	18.72	0.25
15	45	3	45	3	1.41	1.04	2.32	10.14	27.46	1.10
45	90	74	125	77	1.87	1.46	10.37	6.70	27.77	1.94
75	90	78	225	155	2.02	1.05	11.19	7.47	26.13	2.16
110	25	52	250	297	0.11	0.10			0.46	0.74
L ₁		160			0.01					
L ₂		210			0.01					

	Glucose	Phenol Red	Volume
Given	36.00 gm	5.00 mm	250 cc
Recovered	3.74 gm (10.4%)	4.19 mm	207 cc
Absorbed	32.26 gm (89.6%)		43 cc

though the lower duodenal contents, following the instillation of 2% and 5% glucose solutions into the stomach, were practically isotonic throughout the period of study, yet after giving 2% glucose 130 cc. of water were absorbed, while almost the same volume as that of the stomach meal was recovered after the isotonic glucose. From this we may deduce that water is appreciably absorbed by the duodenum only when solutions reach it in hypotonic state. This is supported by comparing the osmolar concentration in the stomach following the 2% and 5% meals. Table V shows that following the 2% glucose meal the gastric contents were hypotonic until the stomach was completely empty. The proximal duodenum, therefore, received hypotonic solutions throughout the test period. Here water was rapidly absorbed so that the duodenal contents were isotonic when they reached the lower duodenum. After a 5.5% glucose meal the gastric contents remaining so much closer to isotonicity throughout the test period reached the duodenum in that state, so that little if any water absorption took place. Value of Phenol Red Indicator.

Unfortunately, phenol red is absorbed or adsorbed to a slight degree by the duodenum and cannot, there-

and 22% to 24%. With the four-lumen tube in place they were instilled intermittently, as described, through lumen 4 (Fig. 2) and collected through lumen 3. When glucose solutions up to 15% concentration were instilled into the duodenum at the same rates there appeared to be a direct relationship between the

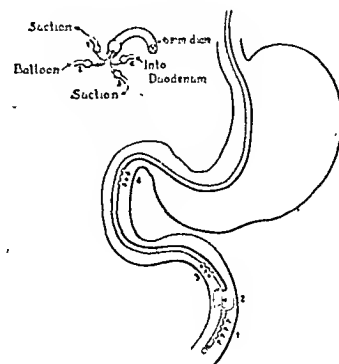


Fig. 2

TABLE IX

R. R. 100

Test Meal 23.3% Glucose—500 cc. into Duodenum

Time	Volume	In	Out	Glucose		Cl ⁻	Total	Phenol Red	
				gm/100cc	gm/100cc			mm/100cc	mm/100cc
0	0	0	0	12.6	0.04	6.00	10.60	26.10	0.75
15	130	130	370	5.75	15.69	20.73	3.36	31.43	1.72
30	130	130	790	7.91	16.45	21.69	3.03	31.74	2.02
45	130	130	610	2.87	5.12	12.91	6.39	26.69	0.46
60	130	130	0	0.01	0.03				0.07
75	130	130	0	0.01	0.03				0.13

	Glucose	Phenol Red	Volume
Given	5310 gm	500 mm	250 cc
Recovered	3336 gm (60.8%)	469 mm	969 cc
Absorbed	2272 gm (29.2%)		-710 cc

fore, be used as an absolute standard against which to measure absorption of water. It is, nevertheless, of considerable aid to illustrate such absorption graphically. Further, it is of inestimable value in detecting any leakage of fluid beyond the balloon during the time of the experiment.

Charts 1 to 4 illustrate the changes in concentration of phenol red observed. Thus, after the 2% glucose meal, one sees the marked concentration of phenol red in the duodenal samples. After the isotonic glucose meal the duodenal concentration was at no time greater than the original meal, although the fact that the duodenal concentration at 30 minutes exceeds even the gastric concentration at 15 minutes, suggests that a little water absorption might have taken place between the 15 and 30 minute period. Following meals of 12.8% and 38.8% glucose, the phenol red concentration in the duodenum always indicated a diluting process.

BEHAVIOR OF GLUCOSE SOLUTIONS WHEN INSTILLED DIRECTLY INTO THE PROXIMAL DUODENUM

In these studies we have limited ourselves to solutions of 2% to 3%, 4.4% to 5.4%, and 13% to 15%,

amount of glucose absorbed and the concentration instilled. This relationship was apparent and not real, because in concentrations below 15% under the conditions of our experiments, practically all of the available glucose was absorbed during the time of the experiment. When a real excess of glucose became available, as in the experiment with the 23.3% glucose, the apparent relationship of absorption to concentration disappeared (Tables VI-IX). Data such as these might lend support to the results of Magee and Reid who found 0.75M (13.5%) the optimum concentration for absorption in the intact gastro-intestinal tract of the rat and cat, and also for the rabbit when instilled into the duodenum.

Thus in Table X we find the following relationship of concentration and grams absorbed:

TABLE X

Conc. Glucose Instilled	% Glucose Absorbed	Grams Glucose Absorbed	Gms. Glucose Absorbed Conc. Glucose Instilled
2.8%	98.7	6.91	2.47
4.4%	99.0	10.59	2.47
14.4%	89.6	32.26	2.24
23.3%	39.0	22.72	0.98

From the standpoint of water absorption the isolated duodenum behaves quite differently from the same duodenum acting in conjunction with the stomach with similar concentrations of glucose (Table XI). Although the glucose solutions were instilled into the duodenum at somewhat slower rates than the stomach emptied a similar meal, we do not believe the difference in time was sufficient to account for the striking differences with regard to water absorption. For example 250 cc. of a 12.8% glucose meal placed in the stomach doubled its volume by the time it reached the lower duodenum, yet the same amount of a 14.4% glucose instilled into the upper duodenum showed a

loss of 43. cc. by the time it reached the lower duodenum. In both instances all specimens recovered from the lower duodenum were virtually isotonic. Comparing the various concentrations of glucose instilled into the duodenum we find again the greatest amount water absorbed from the solution of lowest concentration.

Our data therefore clearly show that experimental results obtained by studying absorption and dilution in isolated intestinal loops cannot be compared with

TABLE XI

Absorption of Glucose and Water
by Duodenum when meal is instilled
into Stomach and Duodenum ———

Conc of Glucose gm. 100 cc	Meal instilled into:			
	Duodenum	Stomach	Duodenum	Stomach
	Glucose absorbed per hour gm.	Total Vol. Recovered c c	Glucose absorbed per hour gm.	Total Vol. Recovered c.c.
2.0			4.1	130
2.8	3.8	36		
5.5			7.6	253
4.4	5.9	82		
12.8			4.1	502
14.4	17.6	207		
23.3	12.7	968		
38.8			8.9	1103

results obtained from studying intact gastro-intestinal segments.

SUMMARY

By the use of three and four-lumen intestinal tubes, we have studied the absorption and dilution of glucose solutions in the stomach and duodenum when

- Retained in the stomach
- Instilled into the stomach, and the stomach and duodenum acted as a complete segment
- Instilled directly into upper duodenum, so that the duodenum acted as an isolated perfused intestinal loop.

The concentrations of glucose solutions studied ranged from 2% to 3%; 4% to 6%; 22% to 24%; and 38% to 40%.

Results:

(1) Considerable amounts of glucose may be absorbed by the stomach alone from solutions of high concentration. From concentrations below 15% no appreciable absorption could be demonstrated.

(2) The importance of the stomach in man as a diluting organ is insignificant in comparison with the duodenum.

(3) When the stomach and duodenum acted as a complete unit, the duodenum showed remarkable versatility in shifting from an organ of glucose absorption to one of glucose dilution.

(4) The importance of the duodenum as a glucose absorbing mechanism is largely a question of the concentration of the glucose ingested.

(5) The best absorption per unit time was usually seen with solutions at or near isotonicity. Although the total absorption per unit time was generally slightly higher from the 38-40% solutions, one must remember that at these concentrations considerable amounts may be absorbed from the stomach. At such concentrations the duodenum acts largely as a diluting organ. With hypertonic solutions the duodenum is capable of mobilizing relatively enormous quantities of fluid in short periods.

(6) The higher the concentration above isotonicity, the greater will be the dilution and the less the actual duodenal absorption. There is no linear relationship between the degree of dilution and the concentration of glucose ingested. There is no appreciable volume change when isotonic glucose is ingested.

(7) Appreciable water absorption occurs only from hypotonic solutions and this absorption takes place in the proximal duodenum.

(8) There is a reciprocal shift of chloride to glucose concentration in the duodenum in the attempt to maintain isotonicity.

(9) When the duodenum is studied as an isolated perfused segment, quite different results were seen from those after gastric instillation of the test meals.

a. Concentrations up to 15% appear to show a linear relationship between concentration and total absorption. This is due to the fact that practically all of the glucose is absorbed during the experiment. When a real excess of glucose is available (after 23.3%) no such relation exists.

b. Absorption of water appears to occur more readily from the isolated perfused duodenum than from the stomach and duodenum acting as a unit.

(10) We do not believe that it is possible to compare data obtained from isolated intestinal loops with those obtained with complete gastro-intestinal segments.

TABLE A

Mouth Meal: 230 cc of 36.3% Glucose

Time Minutes	Stomach Gm/100cc	Vol. cc	Fistula Conc Gm/100cc	Volume at Fistula cc	Gms. Glucose at Fistula
15	23.6	253	3.4	205	6.9
30	19.4	210	5.4	300	16.2
45	9.8	70	6.2	403	26.7
60	3.5	84	2.3	70	1.6

Total Volume at Fistula 980 cc

Fasting Secretion Collected at Fistula
for 30 minute period = 19 cc

(11) A new four-lumen intestinal tube is described which permits the study of isolated intestinal segments in man under physiological conditions.

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DISCUSSION

DR. WILLIAM O. ABBOTT (Philadelphia): May I congratulate the Authors on this very interesting contribution to our understanding of the physiology of glucose absorption. In general confirmation of their findings I may say that rather comparable work which has been going on for some time in Gastro-Intestinal Section of the Hospital of the University of Pennsylvania is leading to very similar conclusions. While there are differences in experimental detail, we too observe absorption to take place from the stomach when solutions of high concentration are given, but not when the concentration used is low. Because there have been so many conflicting opinions, even on this basic point, I am glad to be able to offer this word of confirmation.

DR. HARRY SHAY (Philadelphia): I want to thank Dr. Abbott for his discussion.

DR. A. C. IVY (Chicago): In regard to the authors' paper, I was going to make the remark that it was very interesting physiology, but I could see nothing of practical import connected with the work; however, Dr. Shay has just pointed out that his observations may have a possible application, so that possibility suggests this question: Is there any evidence of irritation of the duodenum or stomach when these hypertonic solutions are introduced into the stomach or duodenum and kept there for a period of time, sufficient to change the blood urea concentration?

A Test for Intestinal Absorption*

By

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INTESTINAL absorption is a function of the digestive tract which has been studied rather extensively in the physiological laboratory, but until recently has been neglected in experimental and clinical medicine. Moreover, unproven assumptions have been made regarding the occurrence of impairment of intestinal absorption in a number of diseases. Consequently, our ideas concerning this function of the intestine in various diseases of the digestive and other systems is not only very incomplete but also unreliable.

Our experimental data demonstrate the potential need for a clinical test of intestinal absorption. These data were obtained by direct experiments on rats which had been fasted for 24 hours to clear their intestinal tracts of food residues, and which were given by stomach tube a known amount of various substances. After a standard period of time, the residue in the digestive tract was determined and the amount absorbed was calculated from it. Figures given in Table I show that the rate of absorption of glucose may be nearly doubled in certain experimental conditions, and reduced to less than one-half of normal in others.

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For a better understanding of the requirements that a clinical test for intestinal absorption should satisfy, it will be necessary to consider briefly the more important factors influencing intestinal absorption. For this purpose a brief review of Verzar's (1) theory of absorption from the intestine is presented, because I feel that at present this is the most workable theory—although neither this nor any other theory has so far succeeded in explaining all known facts.

According to Verzar's concept, substances that are capable of diffusion through the intestinal mucosa are subject to a two-way exchange between the contents of the small intestine and the blood plasma. By the time the contents of the ileum enter the cecum, an osmotic and diffusion equilibrium between the chyme and the plasma has been reached. In the proximal half of the colon this isotonic mixture is subjected to hydrostatic pressure, which forces some of the water into the capillaries rendering the remaining mixture hypertonic. This causes the diffusion of more solids into the blood. The process indicated goes on in the colon until the food residues assume a solid consistency and are expelled as feces with little loss of useful substances. The process of absorption described is accomplished by simple diffusion through a semi-permeable membrane aided by pressure filtration in the colon. For practical purposes, it may be assumed

TABLE I

Intestinal absorption of glucose in rats under various experimental conditions

Experimental Condition	Sex	No. of Rats	Amount Absorbed per 100 gm. of weight	Experimental Condition	Sex	No. of Rats	Amount Absorbed Per 100 gm. of Weight
			mgm.				mgm.
Normal	♂	19	171 ± 14*	Fasting for 48 hours	F	4	147 ± 23
Hyperthyroid	F	8	284 ± 30	Fasting for 72 hours	F	10	158 ± 48
Thyroidectomized	F	4	91 ± 5	Fasting for 96 hours	F	4	151 ± 10
Hypophysectomized	F	17	165 ± 24	Phosphorus poisoning, 6 mgm. per kgm.	F	6	146 ± 9
Adrenalectomized	F	8	78 ± 26	Severe phosphorus poisoning, 8 mgm. per kgm.	♂	4	128 ± 26
Spayed	♂	9	123 ± 26	Dinitrophenol intoxication	F	4	121 ± 25
Normal	M	12	131 ± 12	Hyperpyrexia 40 to 43° C.	F	4	122 ± 23
Castrated	M	10	129 ± 20	Administration of castor oil	F	4	147 ± 16

*Standard deviation.

that most food elements are subject to absorption by this process.

In addition, there are special mechanisms requiring the expenditure of energy which increase the velocity of diffusion of several important substances in the intestine. The most important of these special mechanisms is phosphorylation in the intestinal mucosa, which was suggested by Verzár whose conclusions have been supported in several new ways by studies that we have made (2). Phosphorylation consists of esterification of a substance with phosphoric acid. In the intestine, phosphorylation takes place in the cells of the mucosa. Through constant transformation of the diffusing substance, the gradient for diffusion of this substance into the mucosa is kept high, thus increasing its rate of absorption from the lumen of the intestine. The food elements which at present are known to be susceptible to phosphorylation are utilizable carbohydrates, fats, and Vitamin B₂ together with its precursors. The importance of phosphorylation can be shown (Table II) by comparison of the rate of absorption for xylose, which is not susceptible to phosphorylation, with that for glucose in normal rats and in rats in which phosphorylation has been stimulated by thyroxin or inhibited with phlorizin.

TABLE II

The effects of normal, stimulated and inhibited phosphorylation on intestinal absorption of sugars

Experimental Condition	No. of Rats	Sugar Administered	Amount Absorbed Per 100 gm. of Weight
			mgm.
Normal	8	Xylose	31 ± 3*
Normal	19	Glucose	171 ± 14
Hyperthyroid	8	Glucose	284 ± 30
Normal or hyperthyroid with phlorizin	8	Glucose	34 ± 8
Normal	8	Galactose	187 ± 27
Hyperthyroid	8	Galactose	273 ± 18

*Standard deviation.

Besides phosphorylation, there are several other factors that may influence the velocity of intestinal absorption. Fatty acids must be rendered water-soluble by the hydrotropic action of bile acids before they can diffuse into the mucosal cells to be subjected to phosphorylation.

The concentration of a substance may have a pronounced effect on the rate of its absorption. In general, when absorption of a substance takes place only by simple diffusion, the rate of absorption is proportional to the concentration of this substance. On the other hand, the absorption of substances that are susceptible to phosphorylation is usually independent of their concentration. This is illustrated in Table III by the fact that absorption of alanin was greater from a 10 per cent than from a 5 per cent solution. In contrast, the absorption of glucose from a 20 per cent solution was equal to that from a 5.4 per cent solution.

Changes in gastric emptying also influence the absorption of substances that pass through the mucosa only by simple diffusion. In Table IV it is seen that slowing the rate of discharge from the stomachs of hyperthyroid rats with benzedrine decreased the absorption of xylose to normal. On the other hand, the absorption of glucose remained practically unaffected by changes in the emptying-time of the stomach. The rate of gastric discharge probably influences absorption by altering the intestinal concentration of the substance that is being absorbed.

If before absorption a substance has to undergo hydrolysis, the speed of hydrolysis may be a limiting factor in the velocity of its absorption. This is shown by the comparative rates of absorption of olive oil and of oleic acid in normal and in hyperthyroid rats (Table V).

In the light of this brief outline of the more important factors affecting intestinal absorption, we can define some requirements of a test intended to measure comprehensively absorption in the intestine. The general requirements of any clinical test, before it can be adopted for general use, are that the test must be harmless to the patient, reasonably simple to perform, inexpensive, and not too complicated for performance in an ordinary clinical laboratory. There are special requirements for absorption tests, depending

TABLE III

The influence of concentration on intestinal absorption of alanin and of glucose

No. of Rats	Substance Administered	Concentration	Amount Absorbed Per 100 gm. of Weight
		%	mgm.
8	Alanin	5	36 \pm 5*
8	Alanin	10	96 \pm 6
6	Glucose	5.4	165 \pm 20
4	Glucose	20	168 \pm 12

*Standard deviation.

on whether the test under consideration directly measures the rate of disappearance of a substance from the intestine, or whether the conclusion regarding the velocity of absorption is arrived at indirectly through the concentration or appearance time of the test substance in one of the body fluids or excreta. The following criteria apply to indirect tests of intestinal absorption:

1. The test should be based on the absorption of a substance susceptible to phosphorylation because:

a. Some of the clinically most important food elements are among substances the absorption of which is influenced by phosphorylation;

b. Since permeability is a physical property of the intestinal mucosa whereas phosphorylation is an enzymatic process, it seems reasonable to expect in various pathologic conditions more frequent and more marked disturbances of phosphorylation;

c. Absorption through phosphorylation is only an intensified form of absorption through simple diffusion so that any impairment or diffusion through the intestinal mucosa must be reflected in the absorption of substances susceptible to phosphorylation.

It is unfortunate that all attempts to study intestinal absorption in human beings by indirect methods which have come to our attention have been made using substances such as xylose (3), iodine (4) and various dyes that are incapable of phosphorylation.

2. The substance used in a test of intestinal absorption should be water-soluble.

3. The outcome of the test should not depend on the concentration of the test substance because di-

lution by gastric and intestinal secretions is a variable factor.

4. The test should be independent of the rate of gastric evacuation, which cannot be controlled and is influenced among other things by emotional states.

5. The substance used to measure intestinal absorption should be absorbed as such without preliminary hydrolysis because this introduces the complicating factor of a new enzyme system.

6. The material employed in a test of intestinal absorption should be capable of quantitative determination, and should not occur normally in the medium used for determinations in the test.

7. If the substance used in such a test is utilized in the body or excreted to any extent during the test, it should be possible to determine the rate of its utilization or excretion in order, in doubtful cases, to

TABLE V

Absorption of oleic acid and of olive oil in normal and in hyperthyroid rats

Experimental Condition	No. of Rats	Fat Administered	Amount of Fat Absorbed Per 100 gm. of Original Weight
			mgm.
Normal	10	Oleic acid	271 \pm 44*
Hyperthyroidism	11	Oleic acid	593 \pm 125
Normal	9	Olive oil	453 \pm 29
Hyperthyroidism	5	Olive oil	444 \pm 32

*Standard deviation.

rule out the possibility that abnormalities of these functions are interfering with the test.

TECHNIC OF THE TEST

Forty grams of galactose in 400 cc. of water flavored with lemon juice are administered by mouth to patients who have fasted overnight. Specimens of venous blood are obtained before, and 30 and 60* minutes after, the administration of galactose. The glucose fraction of the blood is removed by fermentation with ordinary (Fleishman's) yeast, as has been described by Raymond and Blanco (5). The residual reducing power of the blood is then determined by the method of Hagedorn and Jensen,

*We also took specimens at 5, 15 and 120 minutes after administration of galactose but found that they yielded little additional information.

TABLE IV

Influence of gastric evacuation on the absorption of dextrose and of xylose from the digestive tract

Experimental Condition	No. of Rats	Sugar Used	Gastric Residue of Sugar	Intestinal Residue of Sugar	Amount of Sugar Absorbed per 100 gm. of Original Weight
			%	%	mgm.
Normal	4	Dextrose	72	28	168 \pm 12*
Hyperthyroidism	4	Dextrose	51	49	292 \pm 24
Hyperthyroidism with benzedrine	3	Dextrose	82	18	274 \pm 7
Normal	4	Xylose	50	50	30 \pm 3
Hyperthyroidism	5	Xylose	11	89	53 \pm 9
Hyperthyroidism with benzedrine	4	Xylose	42	58	35 \pm 3

*Standard deviation.

or any other method used for blood-sugar determinations. The figure for nonfermentable reducing substances in the fasting blood is subtracted from the corresponding figures in the two other specimens to obtain the galactose content of the blood titrated as glucose. In order to obtain the true value for galactose, which has a lower reducing power than glucose, 23 per cent has to be added to this figure.

The test described satisfies our criteria. Galactose, which is chemically very close to glucose, is susceptible to

TABLE VI

Results of the galactose absorption test in 164 patients with endocrine disturbances

Disease	No. of Patients	Outcome of the Test		
		Low 0-12 mg.	Normal 13-30 mg.	High 31-152 mg.
Hyperthyroidism	130		1	129
Myxedema	6	6		
Cushing's syndrome	5	1	3	1
Addison's disease	2	2		
"Hyperinsulinism"	3		2	1
Diabetes mellitus	15	7	6	2
Acromegaly (late)	1	1		
Hyperparathyroidism	1		1	
Menopause	1	1		

phosphorylation (see Table II). It is soluble in water, is absorbed without transformation, can be determined quantitatively and does not occur in the blood. The absorption of galactose, similarly to that of glucose, is within wide limits independent of its concentration in the intestine and of gastric emptying. Galactose is utilized in the body, and changes in the rate of its utilization can be determined by giving galactose intravenously and following the rate of its disappearance from the blood.

The test described was used in 21 normal volunteers and in 232 patients with various diseases, mainly endocrine. From this experience, the normal range for the maximal concentration of galactose in the blood was found to be between 13 and 30 mg. per cent, averaging 19 mg. per cent. Peaks of the galactose curve between 30 and 40 mg. per cent were considered to lie in the borderline high range. Maximal values below 10 and above 40 mg. per cent were considered to be abnormal.

In 10 patients the test was repeated in order to determine the degree of uniformity of its results. In one case the difference between peaks of successive tests was 40 mg.*; in another 21 mg.; in 2 cases 9 mg.; and in 6, 3 mg. or less.

As a check on the galactose absorption test and also as an independent test of liver function, 40 gm. of galactose in 100 cc. of water were injected intravenously in 10 normal individuals and 86 patients with various diseases, chiefly hepatic. Then the rate of disappearance of galactose from the blood was determined. This study, which has not yet been completed (6), indicates that normally there should be no galactose left in the blood 90 minutes following its intravenous injection.

RESULTS

Our clinical results with the galactose absorption test are given in Tables VI and VII. In the first table is shown the distribution of maximal galactose values

in patients with endocrine disorders. So far we have concerned ourselves mainly with disturbances of intestinal absorption in diseases of endocrine organs because our work on absorption was stimulated by certain indications that the thyroid gland exercises considerable influence on absorption from the digestive tract, and because we found by experiments on rats that several glands of internal secretion influence intestinal absorption (Table I).

From Table VI it is seen that in hyperthyroidism the galactose values are consistently high. The average peak of the galactose curve in patients with hyperthyroidism was 67 mg. per cent as compared to the normal average of 19 mg. per cent. Among 130 patients with this disease, the outcome of the test was abnormally high in 124 cases, in the borderline high zone in 5 cases, and normal in one case. It was learned that utilization of this sugar in hyperthyroidism is within normal limits when the galactose is injected intravenously. The accelerating effect of clinical hyperthyroidism on absorption of sugars was also confirmed by a return of the galactose curve to normal after thyroidectomy and by the finding of very low galactose values in the blood of patients with myxedema. The reliability of determination of galactose absorption as a test for diseases of the thyroid gland was found to be comparable to the basal metabolic

TABLE VII

Results of the galactose absorption test in 68 patients with various diseases

Disease	No. of Patients	Outcome of the Test		
		Low 0-12 mg.	Normal 13-30 mg.	High 31-98 mg.
Anxiety states	21	3	14	4
Przet's disease	18		3	15
Osteoporosis	1		1	
Osteosarcoma	1		1	
Congestive heart failure	6		7	1
Intestinal hypermotility (marked)	5	1	3	1
Chronic alcoholism	2	1	1	
Pernicious anemia	2			2
Anemia (severe)	1	1		
Pellagra	1	1		1*
Carcinoma of stomach	1		1	
Anorexia nervosa	1	1		
Hepatic insufficiency	6			6

*After treatment.

rate. This test is particularly useful in cases of hyperthyroidism with a basal metabolic rate under 20 per cent plus and in patients without hyperthyroidism who have an elevation of the basal metabolic rate due to anxiety states with hyperventilation or to cardiac dyspnea. The chief clinical significance of the high rate of intestinal absorption in hyperthyroidism is that glycosuria, postprandial hyperglycemia, and high glucose tolerance curves in patients with this disease do not indicate the presence of diabetes unless a high

*This was in a patient with accelerated absorption due to hyperthyroidism who in two tests had peaks of 90 and 60 mg. per cent. Between the tests the patient was treated with Lugol's solution.

fasting blood sugar is also present. A separate report will deal in detail with these and other aspects of intestinal absorption in diseases of the thyroid gland.

A low rate of intestinal absorption of sugars in Addison's disease is in agreement with the experimental findings in adrenalectomized rats. On the other hand, in Cushing's syndrome the absence of increased absorption of galactose in 4 out of 5 patients does not support the opinion that this syndrome, which in many respects is the clinical opposite of Addison's disease, is due to hyperfunction of the adrenals. It should be added that we were unable to increase the intestinal absorption of glucose in rats by administration of large doses of adrenal cortical extract.

The tendency found to slowed absorption of galactose in controlled cases of diabetes mellitus is of interest but needs confirmation by a larger number of cases. The number of cases of other endocrine disorders in our series was also too small to merit any conclusions.

In Table VIII it is seen that most patients with anxiety states have normal intestinal absorption, especially if we take into consideration that 2 of the 4 patients in the "high" groups actually were in the borderline high zone.

The rather consistent finding of a high rate of intestinal absorption for galactose in Paget's disease (ostitis deformans)—averaging 57 mg. per cent for the 18 cases as compared with the normal average of 19 mg. per cent—was confirmed by a normal or nearly normal utilization of intravenously injected galactose in three patients so tested. The finding of accelerated intestinal absorption which was absent in 3 patients with other diseases producing lesions in bones may be useful in the differential diagnosis of Paget's disease. In the presence of abnormally rapid intestinal absorption of sugars glycosuria, postprandial hyperglycemia, or high glucose tolerance curves do not signify the presence of diabetes in Paget's disease unless there is also a high fasting blood sugar. This apparently removes the rational basis for the routine treatment of patients having this disease with a weighed diet and 15 units of insulin three times a day, which was recently advocated (7) chiefly on the ground that most patients with Paget's disease have impaired glucose tolerance.

Chronic passive congestion due to cardiac failure did not interfere with intestinal absorption in all 8 patients with this condition. This was rather unexpected because cardiac failure is often accompanied by flatulence which is usually ascribed to reduced absorption of intestinal gases into the blood. Another unexpected finding was the absence of impaired intestinal absorption in 4 out of 5 patients with marked hypermotility of the intestine. Marked hypermotility was considered to be present when the head of the barium column at the 6-hour examination of a gastrointestinal series was seen at the splenic flexure of the colon or distal to it. In contrast to this was our finding that the administration of castor oil to rats reduced the absorption of glucose (Table I).

Two patients with pernicious anemia had high values for galactose in the blood following the absorption test. This was rather interesting because impairment of intestinal absorption had been reported in pernicious anemia, and because another patient with a severe secondary anemia had a low galactose curve.

More observations checked by intravenous administration of galactose are obviously needed in the various types of anemia.

A patient with pellagra during the active stage of the disease was absorbing galactose at a very low rate (maximal value 4 mg. per cent). Three weeks later, following successful treatment with nicotinic acid, the peak of the galactose curve was in the borderline high zone (37 mg. per cent).

Six patients with pronounced hepatic insufficiency had abnormally high curves for galactose in the blood. Intravenous administration of galactose showed that impaired utilization of this sugar by the liver was responsible.

COMMENT

Our experience with the galactose absorption test in diseases of the thyroid gland, in Paget's disease and possibly in one or two other conditions where the findings correspond closely to our experimental data indicates that consistent abnormalities of intestinal absorption exist in certain diseases. The remainder of our clinical results are reported at this time mainly for the purpose of showing that the proposed test is suitable for the study of intestinal absorption. It is also apparent from this preliminary report that intestinal absorption in various diseases of the digestive and other systems needs to be studied because some diseases affect intestinal absorption in an unexpected manner.

The fundamental contribution of our work with the galactose absorption test consists of introducing the factor of abnormally increased intestinal absorption into clinical medicine. Heretofore, abnormalities of absorption in the intestine have been associated only with diminution of absorption and the resulting general or specific undernutrition. In the future, the possibility of pathologically accelerated absorption leading to flooding of the blood-stream with certain substances and overloading of organs concerned with the assimilation of these substances, will have to be considered.

Our discovery that the thyroid hormone increases the intestinal absorption of many important food-elements through stimulation of phosphorylation (2) may offer at least a partial remedy for conditions in which decreased absorption in the intestine is due to impaired phosphorylation.

SUMMARY

1. The need for a clinical test of intestinal absorption is demonstrated by data showing that the rate of absorption may be more than doubled in certain experimental conditions having their counterpart in certain diseases of man, and reduced to less than one-half of normal in others.

2. The more important factors influencing intestinal absorption are reviewed.

3. Requirements for an adequate clinical test of intestinal absorption are discussed.

4. The test consists of oral administration of a standard dose of galactose followed thirty and sixty minutes later by determinations of galactose in the blood.

5. Normal standards, and the results of the test in 232 patients with various endocrine, digestive, and other diseases are reported. The most important findings are that intestinal absorption: (a) is increased

in hyperthyroidism and Paget's disease, accounting for certain "diabetic" symptoms seen in these diseases; (b) is decreased in myxedema and Addison's disease, explaining abnormalities of carbohydrate metabolism in these conditions; and (c) is usually unimpaired by hypermotility of the intestine or by chronic passive congestion of cardiac origin.

6. The fundamental contribution of our work with the galactose absorption test is introduction of the concept that intestinal absorption may be abnormally increased in certain diseases.

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DISCUSSION

DR. JOHN L. KANTOR (New York): It is too bad that Dr. Althausen did not have, in his clinical material, some cases of idiopathic steatorrhea. It would have been interesting to see what results his galactose test would give in such definite cases of failure of absorption by the small intestine.

I missed the reason why Dr. Althausen selected galactose and hope he will repeat this in his closing remarks.

DR. A. C. IVY (Chicago): I should like to ask if Dr. Althausen has followed the blood sugar curve as related to urinary elimination. Dr. Althausen has introduced a new concept and it may explain some of the apparent decreases in sugar tolerance in certain diseases. Heretofore, we have said that a decrease in sugar tolerance may be due to a liver disturbance. The diseased liver may not store the absorbed sugar in the form of glycogen and thus a hyperglycemia and perhaps a glycosuria will result.

Is that question clear?

DR. ALTHAUSEN: Yes, it is.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): This appears to be an important contribution to our increasing knowledge of the normal and morbid physiologic processes of the small intestine. The important role of the vitamins in cellular metabolism was emphasized in a recent presentation by E. S. Guzman-Baron, of Chicago. He summarized the collective observations emphasizing the fundamental importance of the vitamins in the digestion and absorption of carbohydrates, proteins, fats and minerals because of their powerful oxidasic and catalytic properties. This explains the rationale of adequate vitamin therapy in disorders of nutrition, especially in disease or dysfunction of the small bowel. The appellation "vitamin" is surely a euphemistic one in view of its powerful chemical attributes.

DR. THEODORE L. ALTHAUSEN (San Francisco): To answer the question asked by Dr. Kantor, galactose was chosen because it is typical of the group of substances the absorption of which is accelerated by phosphorylation, and because it does not occur normally in the blood. For the latter reason, the concentration of galactose in the blood indicates with fair accuracy the rate of its absorption from the intestine. Glucose cannot be used for a test of absorption because the absorbed glucose loses its identity by becoming mixed with the glucose of the blood.

Dr. Ivy correctly pointed out the most important conclusion to be derived from the results of this test in patients with thyroid disease—namely that the so-called "diabetic" type of glucose tolerance curve in patients with hyperthyroidism is in reality due to accelerated intestinal absorption. The same is true of Paget's disease. The finding of accelerated intestinal absorption of galactose has been so constant in our series of patients with Graves' disease that the galactose absorption test is regarded in our clinic as equal in reliability to determinations of the basal metabolism. In addition, the galactose test possesses certain advantages which are indicated in the paper.

As far as the avitaminoses are concerned, we had a single patient with typical pellagra whose intestinal absorption was very much reduced during the active stage of the disease. Three weeks later, after successful treatment with nicotinic acid, the absorptive ability of this patient was better than normal. This is probably another instance in which newly regenerated tissue temporarily exhibits a higher than normal activity.

An Experimental Study of the Effect of the Thyroid on the Motility of the Gastro-Intestinal Tract

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STUDIES on the relationship between endocrine and gastro-intestinal functions has become a matter of increasing interest. Unfortunately our knowledge of this relationship is very incomplete. Although the endocrine problem is gradually being unfolded there is a dearth of scientific work on its effect upon gastro-in-

testinal motility. As a consequence of the latter, many of our ideas are at best mere conjectures. However, a good deal has already been accomplished toward the solution of this difficult problem but obviously, much more remains to be understood and explained. The effect of the thyroid on the digestive tract varies widely depending upon the degree of involvement and the effect of the associated hormonal disturbances. Nevertheless, there is some unanimity of opinion in respect to some of its actions. There can be no question

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that the thyroid gland exerts some influence on gastro-intestinal physiology.

When consideration is given to the relation of dysfunctions of the endocrine system to gastro-intestinal disease the problem becomes even more intricate. For example, definite knowledge is still lacking as to whether the gastro-intestinal disturbances so frequently observed in the endocrinopathies are actually due to the latter or are secondary to changes in the autonomic nervous system. Our work comprises only one phase of this problem and is more in the nature of a preliminary study.

The purpose of our communication in brief is to determine through what mechanism the abnormally act-

relationship there could not be a better understanding of the problem.

Certain suggestions have appeared in the literature concerning the cause and effect of the relationship of thyroid gland to gastro-intestinal motility. The direct effect of thyrotoxicosis on the musculature, the hormonal-metabolic effects and the effects by way of the vagus have been considered as possible methods of action. It is believed by Crotti and others that the endocrine and the autonomic nervous systems are so intimately related that they cannot be studied separately. It is also maintained by Deusch that the thyroid hormone acts only through the nervous mechanism of the gastro-intestinal tract.



Fig. 1 *Right*: Six hour roentgen motility study in the normal dog. The stomach is completely empty. Most of the barium is in lower bowel; the small intestine is empty. *Left*: Motility study in the bilateral vagotomized dog, showing a large gastric retention (at arrow) in six hours.

ing thyroid gland exerts its effect upon the digestive tract. In an effort to answer the simple query whether or not the effect is through the vagus nerves or due to general metabolic changes which secondarily involve the digestive tract, a group of experiments were undertaken on dogs. Gastric acidity studies were not made although we have reported on them in other communications. It was primarily because the literature on this subject is so meagre, confusing and unsatisfactory that it seemed to us advisable to attempt to establish experimentally the relation of the vagus nerve and thyroid gland to gastro-intestinal motility. It also seemed that without a clarification of this re-

Although there are reports of the influence of thyroid action upon the vagus nerve with respect to gastro-intestinal motility considerable academic controversy has arisen concerning this exact mechanism of action and an appraisal of the literature leads only to further confusion and controversy rather than easy evaluation. As early as 1900 Eppinger and Hess had attributed the gastro-intestinal hypermotility in hyperthyroidism to overactivity of the vagus nerve and as recently as 1936 Richieri also believed that the most important pathogenic factor in hyperthyroid gastro-intestinal motility is vagotony produced by direct stimulation of the vagus by the hyperfunction-

ing thyroid gland. Moreover, Rehfuess has reported that small doses of thyroid gland medication exert a stimulating effect on gastro-intestinal function which he believed probably acted through the vagus nerve. In excessive doses, however, it seemed to him that an inhibitory effect was exerted. In several reports, the explanation of gastro-intestinal motor activity in hyperthyroid states has been attributed to a change in gastric secretion. Moreover, the possible involvement of nervous mechanisms in the gastro-intestinal dysfunctions associated with hyperthyroidism deserves consideration. The explanation of an increased gastro-intestinal activity is obviously not immediately at hand.

However, in 1932 Fetter and Carlson studied the effect of induced hyperthyroidism on gastro-intestinal

The relationship of the secretion of the ductless glands and the functions of the vegetative nerves have not as yet been explained with entire satisfaction even with the newer chemical studies. Certain facts, however, have been established, as for example, the influence of the adrenal glands and perhaps also the pituitary thyrotropic hormone in increasing the tonus of the autonomic system. On the other hand, in considering the thyroid some maintain that it acts only through the sympathetic while others suggest that it produces its effect through the vagus, and still others attribute to it both sympathetic and vagotonic actions. Fogelson is under the impression that the thyroid itself does not initiate the increased activity, that the stimulation comes through the sympathetic nervous system and that the most powerful control of the



Fig. 2. *Left.* Normal motility of the gastro-intestinal tract in six hours. The stomach is completely empty. The barium is scattered through the lower ileum and large intestine. *Center.* Same animal, thyroidectomized, illustrating the effect of thyroid medication on the intestinal tract. Roentgenogram after seven days treatment during which time 350 grains of desiccated thyroid had been administered shows the stomach empty and very little change in the motility of the intestines. *Right:* Roentgenogram after ten days of thyroid medication (500 grains of desiccated thyroid) shows some acceleration of motility of the intestinal tract.

motility in the non-vagotomized dog and found that the motility was increased. Later Fetter, Barron and Carlson sectioned the vagus nerves below the diaphragm and then fed sufficient thyroid to produce hyperactivity of the gland and found that gastro-intestinal motility was again accelerated. Their experiments indicated that thyroid activity apparently did not take place through the vagus nerve and they therefore regarded it as clear that the influence of the thyroid on gastro-intestinal motility is largely, if not wholly, independent of the possible influence of the thyroid hormone on the gastro-intestinal vagus mechanism. This work raises the question as to the part played by the stimulated intact thyroid gland and especially by what mechanism such action takes place.

sympathetic system is in the adrenal glands. Furthermore, the need for the elaboration of the action of the thyrotropic pituitary hormone in connection with this problem is manifest.

Timme recently re-emphasized his belief that the thyroid rarely functions alone and that any disturbance of this gland always induces a change in the function of other glands. He points out in general, that whenever thyroid dysfunction exists the involvement no longer remains entirely confined to it but becomes a multiglandular disturbance. Again, it is evident that our knowledge regarding the action of the endocrines upon the gastro-intestinal functions is still far from clearly established, especially since the

problem of polyglandular involvement is so difficult of approach.

It seemed to us that the removal of the thyroids (and parathyroids) would interrupt the so-called endocrine chain and thus interfere with interglandular communications. Such a procedure was one of our approaches to our problem which may now be stated as follows: in hypermotility of the digestive tract does the thyrogenic effect of the thyroid upon the autonomic nervous system play a significant role or is it the effect of gastric secretory changes or is it simply the result of the greatly heightened metabolic rate?

In this introductory presentation we are concerned only with the relationship of the thyroid gland to the vagus nerve and their effect upon gastro-intestinal motility. As will be pointed out, the work of others was repeated but in addition we have performed total thyroidectomy (and parathyroidectomy) so as to remove any effect through a pluriglandular mechanism either by way of nerve or through a purely thyroid or secondary endocrine gland stimulation.

A group of dogs with suitable controls were utilized in these experiments. Total thyroidectomies were performed in each animal. Both vagus nerves were severed at the lower end of the esophagus below the diaphragm. In the feeding of desiccated thyroid relatively large doses were administered. The dosage was 0.4 gm. (and in some instances, more) per kilo of body weight. All the animals so fed lost weight. After the cessation of treatment the animals regained their weight. A number of our dogs developed parathyroid spastic states which necessitated the injection of parathormone as well as the administration of calcium for a brief time. The parathyroid deficiency was controlled in this way and therefore could not have had any significant influence on the final results.

NORMAL MOTILITY STUDIES

In a series of eight dogs in which normal gastro-intestinal motility was studied, the stomach was found completely empty in the six hour examinations following the administration of barium; a small amount of barium was frequently noted in the lower ileum and the head of the barium meal was usually observed in the descending colon. Desiccated thyroid administered to normal dogs produced an acceleration of gastro-intestinal motility. The small intestine was completely emptied and most of the barium meal had been evacuated with only a small amount remaining in the colon.

MOTILITY STUDIES FOLLOWING BILATERAL VAGOTOMY

Bilateral vagotomy was performed in a series of thirteen animals. In eight of these the normal motility had been previously studied. After a post-operative recuperative period of from 10 to 21 days, studies were made on the effect of vagotomy on gastro-intestinal motility. In the 6 hour examination of this group a gastric retention was invariably found in almost every instance. The barium was scattered through both small and large intestines and the head of the barium meal was usually found to be in the descending colon. It is interesting to point out that

the motility of the intestines was not significantly affected by the bilateral vagotomy.

EFFECTS OF THE ADMINISTRATION OF DESICCATED THYROID IN VAGOTOMIZED ANIMALS

In a series of five vagotomized dogs, desiccated thyroid was administered orally. Subsequent study showed a definite thyroid action on the motility of the gastro-intestinal tract in that the motility was greatly accelerated in every instance. In the 6 hour examination, following vagotomy, there was a gastric residue whereas, after a period of thyroid medication there was complete emptying. The small intestine was completely empty and the colon had evacuated most of the barium. However, a small amount of barium still remained in the colon. This demonstrates conclusively that thyroid action is independent of the vagus nerves, an observation which is in accord with the findings of Fetter, Barron and Carlson.

STUDIES OF MOTILITY IN THYROIDECTOMIZED ANIMALS

In a series of six animals total resections of the thyroid were performed in order to determine what effect the removal of the thyroid alone had upon the motility of the gastro-intestinal tract. It was observed that the removal of the thyroid had no immediate effect upon gastro-intestinal motility. In the six hour roentgen examination, the stomachs were completely empty. Within a period of from 10-21 days following thyroidectomy, the motility of the intestines was not significantly affected. In several animals a sluggish motility of the intestines was noted. This experiment gave conclusive evidence that the removal of the thyroid gland alone did not in any way significantly affect the normal motor physiology of the digestive tract in the immediate studies. However, in two additional dogs observed over a period of 5 months, there was a constant gain in weight and the development of myxedematous features. With this development, which in itself produced sluggish motility with loss of tone of the digestive tract, a superimposed bilateral subdiaphragmatic vagotomy was followed by gastric dilatation resulting in a greater gastric retention than was observed in the animals which had only been vagotomized. The injection of one cc. of thyroid extract administered daily for 16 days decreased the retention by two-thirds and it was clear that if sufficient thyroid extract was given the retention could be entirely overcome.

MOTILITY STUDIES IN VAGOTOMIZED AND THYROIDECTOMIZED DOGS

In six vagotomized dogs, all of which showed a gastric retention, a total thyroidectomy was done. A gastro-intestinal roentgen study revealed a similar picture to that obtained in the vagotomized animals. In every instance a gastric residue was still observed. In the immediate examination, between 10 and 18 days postoperatively, the motility of the intestines was variable but on the whole showed no significant change from that of the normal. These findings gave definite proof that the removal of the thyroid gland in vagotomized animals did not have any immediate effects upon the gastro-intestinal motility other than those seen following vagotomy alone.

THE EFFECT OF DESICCATED THYROID ADMINISTERED TO COMBINED VAGOTOMIZED AND THYROIDECTOMIZED ANIMALS

In six animals in which a bilateral vagotomy and thyroidectomy were done desiccated thyroid was administered orally. After 7 days of thyroid medication

the motility was slightly increased with a reduction in gastric retention but varying periods after 10 days the stomach was completely emptied and all of the animals presented marked hypermotility of the entire gastro-intestinal tract with the production of a number of bowel movements. Four weeks later after



Fig. 3. *Upper Left*: Thyroidectomized animal revealing a sluggish motility of the intestinal tract in the six hour roentgen examination. The stomach is completely empty, all of the barium is in the small intestine, and none in the colon. *Upper Right*: Same animal, 29 hour examination reveals expulsion of the barium with most of the meal in the lower left colon. *Lower Left*: Same thyroidectomized dog following double vagotomy. Note the large (6 hour) gastric retention with sluggish motility of the intestinal tract. *Lower Center*: Same animal, 31 hours after administration of barium showing an unusually large gastric retention. *Lower Right*: Same animal, 55 hours later, still showing a large gastric retention. This latter is not the usual finding.

cessation of thyroid medication re-examination of these animals revealed a return of the gastric retention.

CONTROLS

As a check and control to these experiments the above procedures were reversed, i.e., in four animals thyroidectomies were performed first. Subsequent roentgen studies on motility revealed no immediate effect upon the gastro-intestinal tract. Bilateral vagotomies were then performed on these animals, with the result that a gastric retention occurred in each instance. The above findings were exactly similar to those observed in the original experiments described.

SUMMARY

The physiologic mechanism of thyroid action upon the gastro-intestinal tract has not been clearly established in the past. A preliminary study was made to determine the effect of the thyroid and the vagus nerves on gastro-intestinal motility in dogs. Our studies yielded the following results:

1. Desiccated thyroid administered to normal dogs showed an acceleration of gastro-intestinal motility.
2. Motility of the stomach is invariably affected by section of the vagus nerves. This procedure causes a six hour retention in almost every instance.
3. Motility of the intestines is not significantly affected by section of the vagus nerves. The immediate effect of vagotomy on the digestive tract is mainly on gastric motility with very little, if any, effect upon the intestines.
4. Desiccated thyroid administered to vagotomized dogs revealed an acceleration of gastro-intestinal motility thus demonstrating conclusively that thyroid action is independent of the vagus nerves.
5. Removal of the thyroid glands alone had no immediate effect upon gastro-intestinal motility. After a lapse of months, however, it did produce some loss of tone and sluggish motility.
6. Thyroid gland extract given subcutaneously or desiccated thyroid administered orally to the thyroidectomized animals accelerated gastro-intestinal motility.
7. In the combined vagotomized and thyroidectomized dogs, motility studies revealed no immediate changes other than those noted in the vagotomized animals (6 hour gastric retention) indicating that thyroid removal did not influence the changes noted following vagotomy.
8. Desiccated thyroid administered to the animals with combined vagotomy and thyroidectomy revealed a hypermotility of the gastro-intestinal tract with the return of retention after cessation of thyroid medication.
9. Thyroid medication in adequate dosage produced an acceleration of motility of the intestines as well as the stomach.

CONCLUSIONS

The administration of adequate doses of desiccated thyroid gland to dogs with and without the removal of the thyroid gland produces the same effect whether the vagus nerve is intact or not. In other words, induced hyperthyroidism increases gastro-intestinal motility with or without sectioning of the vagus nerve.

Removal of the normal thyroid gland has no immediate effect upon the motility of the gastro-intesti-

nal tract but when myxedema supervenes there is evidence of loss of tone throughout the gastro-intestinal tract.

Bilateral section of the vagus nerve produces a gastric retention which can be overcome by thyroid medication.

A combination of a thyroidectomy and a bilateral vagotomy in the same animal is followed by an immediate picture which duplicates that of bilateral vagotomy alone.

Therefore, it has been definitely shown that the effect of increased thyroid action upon gastro-intestinal motility does not occur through the vagus nerve but is entirely independent of it.

Since thyroid medication in amounts adequate to produce the hyperthyroid syndrome in the absence of the thyroid gland, is followed by increased gastro-intestinal motility it would seem that heightened basal metabolic activity probably accounts for the change. Since pluriglandular action has been disturbed by thyroidectomy it would seem likely that any other hormonal action through the thyroid gland is improbable though by no means impossible.

In this report we make no effort to evaluate the possible roles played by the pituitary thyrotropic hormone nor the adrenal glands nor have we sufficient data to clarify the mechanism of pluriglandular activity in its relation to gastro-intestinal motility. In further studies we hope to clear up some of these involved problems.

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DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore): For a long time considerable interest has been manifested in the relation of the endocrines to gastro-intestinal function. It is well known that certain digestive symptoms are produced by disturbances of these glands. Inasmuch as the thyroid is one of the most important of the endocrines, the digestive symptoms manifested as the result of its dysfunction have been carefully studied and their clinical significance has become more clearly recognized. It is well known, for instance, that hyperthyroidism is frequently associated with diarrhea and hypothyroidism with constipation; but the exact mechanism by means of which these manifestations are brought about have by no means as yet been fully established.

In an attempt to unravel this intricate problem, Doctor Morrison and Doctor Feldman have conducted their experiments, which tend to indicate that the changes in mo-



Fig. 4. *Upper Left*: Demonstrates a (six hour) gastric retention (at arrow) in a bilateral vagotomized dog. All of the barium is in the small intestine and none in the colon. *Upper Right*: Combined double vagotomy and thyroidectomy in the same animal illustrating a gastric retention in six hours with barium scattered through the small and large intestine. *Lower Left*: Thyroid medication in the combined vagotomized, thyroidectomized dog, treated for seven days (280 grains desiccated thyroid), showing a small gastric retention (at arrow) with most of the barium in the colon. *Lower Center*: Same animal treated for ten days (400 grains desiccated thyroid) revealed complete emptying of the stomach with marked hypermotility of the intestinal tract in the six hour roentgen examination. *Lower Right*: Same animal, showing a return of the gastric retention (at arrow) after a rest period (no medication) of 25 days.

tility of the gastro-intestinal tract, induced by thyroid action, are not influenced by way of the vagus or sympathetic nervous system.

But the problem is not simple for, as Timme and others have also pointed out, the thyroid rarely functions alone and the disturbance of this gland induces a change in the functions of the other glands, such as the parathyroids and pituitary, in other words, a multi-glandular endocrine involvement occurs.

In a further study of this larger problem, which is being conducted, Doctors Morrison and Feldman will attempt more fully to clear up the significance of this multi-glandular relationship to the associated digestive dysfunction.

Thank you!

DR. THEODORE ALTHAUSEN (San Francisco): I was very much interested in the observations of Drs. Morrison and Feldman on the increased emptying rate of the stomach and increased motility of the intestine under the influence of the thyroid hormone. In working with hyperthyroid rats, we made similar observations and were able to determine quantitatively the acceleration of the gastric discharge. Normal and hyperthyroid rats were given by stomach tube a 20 per cent solution of glucose or xylose. One hour later the rats were sacrificed and the amount of residual sugar determined separately in the

stomach and in the intestine. In normal rats, 72 per cent of the unabsorbed glucose was found in the stomach and 28 per cent in the intestine. In hyperthyroid rats, only 51 per cent of the remaining glucose was in the stomach, whereas 49 per cent of it was in the intestine. This effect of the thyroid hormone was even more pronounced when we fed to rats xylose, which has a slightly irritating action. Normal rats had 50 per cent of the residue in the stomach and 50 per cent in the intestine, while in hyperthyroid rats only 11 per cent of the residue was found in the stomach and 89 per cent in the intestine. These findings are rendered more significant by the fact that the rate of intestinal absorption for these two sugars is approximately doubled in hyperthyroid rats.

It is of interest that the slowing of gastric emptying in hyperthyroid rats with benzedrine did not significantly reduce the rate of intestinal absorption of glucose.

An increase of intestinal motility in our hyperthyroid rats was manifested by a tendency to develop diarrhea after the feeding of such slightly irritating substances as xylose or oleic acid. This tendency was entirely absent in normal animals.

DR. SAMUEL MORRISON (Baltimore): I thank those who have discussed the paper, and I have nothing further to add, thank you.

Editorials

NEW RESEARCHES ON THE MECHANISM UNDERLYING HEADACHE

ONE of the remarkable peculiarities of medical practice is that almost nothing is known about the mechanics of the commonest symptoms, and usually but little research is ever done on the subject. Who ever heard of anyone's getting large sums of money from a foundation to study mucous colitis, or ordinary headaches, or backaches, or nervousness, It isn't done. Enormous sums are spent commonly for research on rare diseases, simply because they excite most interest. For instance, recently all the public health forces of a great state were marshalled to fight an epidemic of *fourteen cases* of a rare type of encephalitis. Large sums of money were obtained from the state and the federal government; a large number of WPA workers were assigned to make surveys of mosquitoes and birds, and every effort was to be made to wipe out the disease. As we sat in a meeting and heard this great campaign being explained to the physicians gathered for the state medical convention, we could not help wondering how many hundreds of thousands of invalids there were in that state, crippled and suffering and kept on relief rolls or in charity hospitals because of such common troubles as constitutional inadequacy, psychopathy, constant fatigue and weakness, backache, headache, hypertension, and arthritis. We wondered if anyone could ever get much money with which to study these tremendously important and common scourges of civilized man.

Because of thoughts along this line, we were particularly pleased to see recently a report of a paper by George Schumacher and Harold Wolff on experimental studies on headaches and the pathways over which pain travels. It is to be found on page 488 of the July number of the *Journal of Clinical Investigation*.

Using volunteers, these investigators regularly pro-

duced a bilateral type of headache by injecting 0.1 mg. of histamine phosphate intravenously. They could see, then, what difference was made by the previous section or destruction of one or more nerves of the face or scalp or neck. Some of the volunteers studied had submitted to surgical operations on one of these nerves, and others had suffered some injury to the brain stem or to dorsal roots which resulted in partial or incomplete analgesia of one side of the back of the head.

It has been shown that histamine produces headache by causing dilation of cranial arteries, hence the origin of the nerve stimuli was known. It was found that four patients who, as a result of *incomplete* section of the trigeminal sensory nerve root, had unilateral loss of sensation over the lower part of the face, still had headache on both sides of the face and head. Five patients who, as the result of *complete* section of the trigeminal sensory nerve root, had in addition to hemi-analgesia of the lower half of the face, unilateral loss of sensation over the frontal, temporal, and parietal areas, did not get a histamine headache in these regions, although they did get it elsewhere over the head.

That ligation of the middle meningeal and temporal arteries, done at the time of a trigeminal root section, was not the cause of the absence of the histamine type of headache was shown by the appearance of a histamine headache after ligation of the vessels and only partial transection of the nerve root.

Two patients who had a unilateral loss of sensation in the occipital region did not have headaches induced in this region by histamine. They did, however, have headaches elsewhere in the head.

Other observations indicated that there were additional, though less important, afferent pathways. In short, painful messages coming from distended cranial arteries of the front of the head and traveling along

the sensory root of the fifth cranial nerve, were mainly responsible for frontal, temporal, and parietal headaches. The upper cervical sensory roots carrying sensation from the cranial arteries in the back of the head were chiefly responsible for occipital headaches.

Walter C. Alvarez, Rochester, Minn.

THE UNRELIABILITY OF GASTRIC ANALYSIS AS AN INDEX TO PROGNOSIS IN CASES OF PEPTIC ULCER

THE average physician, and even some gastroenterologists, appear to cling to the idea that the amount of free acid found in the stomach, after even one test meal, can serve as an index to the mildness or intractability of an ulcer and to the way in which it will respond to medical or surgical treatment. Actually, Vanzant et al showed a few years ago by following up a fairly large series of cases, that there is no statistical justification for this point of view. They found no close correlation between the height of the acidity and the intractability of the lesion, and it was obvious that by measuring gastric acidity one could not pick the patient who would do badly after operation. Furthermore, high acidities were found to be of no value in the diagnosis of ulcer because high acidities are commonly found in tense persons with indigestion in whom an ulcer cannot be demonstrated.

Bloomfield and French (Jour. Clin. Inves., 17:667, 1938) have recently come to similar conclusions after a study of what they call basal gastric secretion. To estimate this they keep the patient at rest in a warm bed and give him no food for at least twelve hours. The gastric contents are then withdrawn at ten-minute intervals for an hour or two or until the secretory rate becomes fairly constant, and it can be assumed that a basal level has been reached. Repeated tests of this type made on normal persons showed that the secretory rate is fairly constant for the individual.

Interestingly, in one-third of the nine cases of gastric ulcer studied no free acid was secreted. Some of the patients with duodenal ulcer poured out a juice with an acidity as high as 140. Even with the small number of cases analyzed, Bloomfield and French felt they could state definitely that there was no correlation between the rate of healing of an ulcer and the degree of acidity of the stomach. They concluded that "acidity is certainly not the major determining factor."

Walter C. Alvarez, Rochester, Minn.

IS IT WISE TO GIVE A PURGATIVE TO A PERSON COMING DOWN WITH A COLD?

AS we showed many years ago in "Surgery, Gynecology and Obstetrics" for June, 1918, the giving of a cathartic at the beginning of any medical or surgical treatment is a relic of ancient Greek medicine, and is based on the idea that hurtful humors must first be cleaned out of the body before any healing procedure can be carried out with hope of success. As is the case with many human customs, this one continued for hundreds of years after the theory on which it was based was given up and largely forgotten.

Now come Colonel Smith and Captain Baier, in the "Military Surgeon" for January, 1939, with a report of a study carried out to see if it really does help to give castor oil or magnesium sulfate to a soldier when

he is coming down with an acute upper respiratory tract infection. As Smith and Baier say, during the last twenty-five years the medical profession has gone a long way toward giving up this ancient practice, and some authorities now actually forbid it.

The study here commented on was carried out over a period of three years, during which time the physicians studied enlisted men on sick report at Fort Benning, Georgia. During this period there were three epidemics of respiratory disease during which 1013 cases were studied. In 303 cases the treatment was begun with a dose of castor oil, in 217 magnesium sulfate was given, and in 493 there was no purgation.

The figures show clearly that the purged soldiers lost their fever more slowly than did those men who were not purged, and purgation definitely delayed the return of the soldiers to duty. Ninety per cent of the men who were not purged were back on duty in four days, as compared with 79 per cent of those who had castor oil and 79.3 per cent of those who had magnesium sulfate.

Colonel Smith and Captain Baier concluded, then, that the best treatment for the respiratory infections is probably rest in quarters with forced fluids, restriction of diet, local treatment to the nose and throat, and ammonium chloride troches as indicated. Small doses of salicylates were used to relieve aches and pains.

It would be well if these officers would now make another study to find out whether the forcing of fluids, the restriction of diet, or the local treatments are of any value. The chances are large that they are not; perhaps they also are harmful.

Walter C. Alvarez, Rochester, Minn.

QUESTIONNAIRE ON FATALITIES DUE TO GASTROSCOPY

IN his "Clinical Gastro-Enterology" (St. Louis, Mosby, 1939) H. W. Soper wrote, concerning gastroscopy that "A considerable number of fatalities have occurred." It seemed to me that Dr. Soper must have been thinking of the experience with the old rigid gastroscopes. Dr. Soper has since written me that he knows "of no fatality with the use of the Wolf-Schindler Gastroscope." The use of rigid gastroscopes was certainly dangerous, and because of this the flexible gastroscope was constructed. I believe this instrument would be safe even in the hands of an awkward examiner if he were to be guided by the few contraindications. However, one occasionally sees the statement that gastroscopy is a dangerous method, and Renshaw, an expert gastroscopist, doubts the safety of the flexible gastroscope in the hands of an untrained physician.

However, in spite of all my efforts, I have been unable to hear of a single fatality due to the use of the flexible gastroscope. I realize that I am not able to keep in close touch with all specialists using this instrument, and it is well known that disagreeable accidents are seldom published immediately.

Gastroscopy has opened a new field of gastric pathology, and if it is to be used daily by the gastroenterologists as a routine method, as I believe it should be for the early diagnosis of gastric carcinoma, we should know if it involves any danger to the life of the patient. Perhaps it is surprising that no fatalities have yet been reported because fatalities due to inept

proctoscopy are well known, and even the X-ray examination is not quite harmless. Perforation of a gastric ulcer has occurred during strong palpation of the lesion back of the screen.

But even if a death occurs, it may be hard to prove that the instrumentation alone caused the disaster. Moutier published the case of a patient who, scheduled for gastroscopy, suffered a perforation of his ulcer the night before the examination. If this perforation had occurred twelve hours later the gastroscopy would doubtless have been held responsible for the man's death. If, considering all the dangers, a gastro-enterologist should decide to gastroscop a patient suffering from angina pectoris, and the patient should get an attack during the examination and die, the amount of blame to be ascribed to the instrumentation would be hard to establish.

In order to get at the facts, I am here and now asking all colleagues who are using the Wolf-Schindler gastroscope to write either to me or to the editor of this journal answering the following questions:

(1) Have you ever observed a death, following gastroscopic examination, which you attributed to traumatism caused by the instrument? Were the recognized contraindications excluded?

(2) How many gastroscopies have you carried out?

I will try to place these questions in the "Arch. F. Verdauungskrankheiten." (Now appearing in Basel), in the "Arch. d. Maladie d. L'Appareil Digestif," and in the Japanese "Folia Gastro-Enterologica." The results of this questionnaire, if there are any, will later be published. Names will be omitted. It is evident that a prompt reply is not only in the interest of our patients but of the method and of all gastroscopists. Only complete frankness can prevent gastroscopy from

sharing the fate of cystoscopy, which for thirty years was a suspected and opposed method of examination.

R. Schindler, M.D., Chicago, Ill.

A POSSIBILITY IN THE STUDY OF THE SEVERAL FRACTIONS OF GASTRIC ACIDITY

ONE of the things most to be desired in the study of gastric secretion is the identification and separate analysis of the several constituents of the gastric juice. There are at least four different types of cells in each gastric fundus gland. As Hollander showed, the secretion of the parietal cell appears to be practically nothing else but hydrochloric acid and water. It is thought that the secretion of the chief cell contains pepsin, salts and water. The neck cells probably produce a fluid containing mucus and salts, and the foveal cells produce probably the flocculent type of mucus. By graphing certain data and then extrapolating, Hollander and others have gotten a pretty good idea of the composition of the alkaline or neutral secretion of the stomach.

It may be worth noting that Bickel, in 1905, made what may prove to be a very useful observation. In volume 42 of the *Berliner klinische Wochenschrift*, Bickel reported that in the fourth stomach of the goat the two types of juice, one alkaline and the other acid, are secreted alternately. The basic alkaline juice was secreted while the animal was fasting, and the acid secretion came when it was fed. These changes could be shown in a Pavlov type of pouch made from the fourth stomach. The great advantages of studying gastric secretion in such an animal must be apparent to every experimentalist.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

Studies on the Changing Incidence of Peptic Ulcer. By Gunnar Alsted, Copenhagen, Ejnar Munksgaard, 148 pp., 1939. Price d. Cr. 11.20.

THIS is a thought-producing little book based on some remarkable data which have been collected in Denmark during the last thirty years or more. If we could only understand what these data mean we could probably know much of what we need to know about the causes and means of prevention of ulcer. It appears that the incidence of chronic ulcer has been increasing rapidly in men while it has been steady or falling off slightly in the case of women. As a result, during the years the male to female ratio has been changing from less than 1 to 1 to about 3 to 1, as it is here in the United States. There has also been a tremendous change in the ratio between gastric and duodenal ulcers, so that whereas formerly most of the ulcers were gastric, now there are ten or more duodenal ulcers to one gastric ulcer.

There is much evidence to indicate also that thirty years ago ulcers tended to be acute and not chronic. Hence the older clinicians were perhaps justified in their view that they could cure patients with ulcer. Nowadays about all a gastro-enterologist hopes to do is to heal the ulcer that is present at the time the patient comes. That it will break open again some day is expected.

Another remarkable fact brought out by Dr. Alsted's statistics is that if one plots the incidence of hematemesis as ordinates and the figures for the growing population of Copenhagen as abscisses, one gets a curve which rises slowly up to the year 1917. Then there is an abrupt and marked fall, and after that there is a much more marked rise in the curve, a rise which is much steeper in the case of the men than in the case of the women. In the case of the men the curve is now almost a vertical line. As one would expect, there has been in recent years a tremendous increase in the incidence of melena, with again a more nearly vertical line for the figures for men.

Alsted perhaps wisely does not attempt to theorize very much as to the possible causes for these remarkable changes in the incidence of peptic ulcer.

Le Cancer de l'estomac au début. By René Gutmann, Ivan Bertrand and Th. J. Péristiany: Etude clinique, radiologique et anatomo-pathologique. Paris, G. Doin et Cie., 493 pp., 563 illustrations, 1939.

THIS beautiful volume marks the culmination of Dr. Gutmann's and his associates' years of study of the earliest manifestations of cancer of the stomach. Any book that is based on years of fact-gathering and study is likely to be good, and this is

no exception to the rule. It is to be hoped that the volume will be translated into English so that many more physicians can profit from its teachings.

It is a joy to find at last a book written on the *beginnings* of cancer of the stomach—on the first symptoms and on the first signs. Usually in the past the textbook descriptions have been of gastric cancer in its terminal and incurable stages, and unfortunately physicians have become so used to these descriptions that when a few men began to describe the lesions in their earliest stages their papers were either ignored or else misquoted, misinterpreted and scorned; even yet the authors of these descriptions are being accused of calling all sorts of lesions cancerous when they were no such thing.

Gutmann and his associates first describe what they call latent or puzzling forms of gastric cancer. As they say, many patients are seen with curious first symptoms. Some come (1) with an epigastric tumor but no symptoms, (2) with the first symptoms due to metastases, (3) with edema as the first symptom, (4) with nothing but vague indigestion, (5) with indigestion which is easily relieved at first by treatment, (6) and others complain only of loss of appetite, vomiting, nausea, dysphagia, air swallowing, hemorrhage, hunger pain, anemia, constipation, diarrhea, fever, loss of weight, or loss of strength.

In chapter 3 the authors describe the painful ulcer-type of beginning cancer, and they attempt to differentiate ulcers which begin benignly and become cancerous, and those which begin as cancers and become ulcerated. They present many short case histories to illustrate these types of cases, and they show that some malignant ulcers will, for a time, appear to heal under medical treatment.

It is a pleasure to find the authors showing roentgenograms of what look like typical benign ulcers of the stomach and admitting that some of these lesions later proved to be malignant. There was no way of telling one from the other at the beginning. The only regret the reviewer feels about the book is that the authors do not seem to be conversant with the large amount of work done on this topic in this country and the need for placing emphasis on the fact that the problem in early diagnosis of carcinoma of the stomach is not to determine how many benign ulcers turn into cancers but how many ulcer-like lesions are cancerous when first seen by the physician.

To show how frequently one sees early ulcer-like lesions, Gutmann and his coworkers state on page 52 that during the last 300 gastrectomies per-

formed in their clinic, there were removed:

- 85 ordinary vegetative cancers
- 133 benign gastric ulcers
- 43 ulcers which had apparently begun benignly and had later become malignant, and
- 39 ulcer-like cancers.

The book contains a beautifully illustrated section showing the earliest radiologic signs of cancer. There one finds described and illustrated the several types of niches and plateaus, and the peculiar conical deformity of the pars pylorica.

Gutmann is apparently conservative

as to his histologic criteria of cancer, and in sections he likes to see all of the several cellular changes which are characteristic of malignancy. He does not appear to be acquainted with the quick staining of frozen sections described and used to such advantage by MacCarty, Broders, Terry and others.

It is a pleasure to find Gutmann admitting that gastric analysis is of little value in diagnosing early carcinoma of the stomach. As he says, it can't be relied on.

Gutmann knows that gastritis is common in stomachs that show

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cancerous changes, and he recognizes precancerous gastritis, but he does not believe that "classical chronic gastritis" is a precancerous lesion, and he wouldn't think of resecting a stomach with this lesion simply to avoid the danger of cancer.

There is so much good material in this book that it cannot all be commented on. Suffice it to say that here is a book to be studied and enjoyed by all studious gastro-enterologists. Would that its message could be spread widely to all the physicians of the world. We compliment Dr. Gutmann and his associates and rejoice with them in the publication of this fine work.

Diseases of the Intestine. By Raoul Bensaude and collaborators. Vol. IV. Masson & Co., Editors, Paris.

This fourth volume, last of the treatise devoted to intestinal pathology, was barely finished before Raoul Bensaude's premature death. His pupils and co-workers have dedicated it to his memory. It deals particularly with the various affections of the ano-rectal segment. Hemorrhoids and rectal bleeding have always attracted attention from the medical world, long before Hippocrates. Keenly interested in the ever-changing conception throughout the centuries about the pathological significance of these ailments, the authors

have written a most elaborated chapter concerning the historical part of the question. On the matter of the differential diagnosis, they insist on the necessity of a complete examination, including careful anamnesis, inspection of the anal region, eversion of the rectal mucosa, digital examination and proctoscopy. This procedure is the only way to avert fatal errors. The treatment of hemorrhoids, conceived along the ordinary lines, can be thus summarized:

1. Local and general hygiene, a restrictive diet, regular emptying of the bowels are the first steps to be taken about the management of the light accidents, along with local application of soothing ointments, suppositories, etc.
2. Sclerosing injections with quinine and urea is the first choice treatment of bleeding and slightly prolapsed internal hemorrhoids. This method, tried by the authors over a twenty year period with gratifying results, is particularly developed in their book.
3. Second degree prolapses and intensive bleeding from mixed hemorrhoids will also benefit by the injection therapy, followed by monopolar electro-coagulation.
4. Surgery and surgical electro-coagulation must take care of the more serious cases.
5. External thrombotic hemorrhoids require immediate surgical excision; thrombotic mixed hemorrhoids are, on the contrary, almost instantly relieved by roentgenotherapy.

Diagnosis of fissure in ano requires a complete and delicate examination. Physiotherapy, by means of high-frequency short-wave and X-rays is the best treatment, along with perissural injection of different solutions, such as quinine and urea, glucose, oil, etc. *Pruritus ani* may be initiated by various systemic diseases, jaundice, leukemia, Hodgkin, diabetes, digestive ailments; local causes are, of course, the predominant factor, especially hemorrhoids. *Pruritus ani* being a tenacious and recurrent ailment, treatments advocated are numerous and in many cases fail to bring any permanent or satisfactory relief. After dealing with local therapy, autohemotherapy, surgery and physiotherapy, they point out the surprisingly good results obtained by local "histamine" injections, tried on some 300 patients. *Ulcerative rectocolitis*. In the opinion of the authors, no medical writer has yet succeeded in turning up a clear and comprehensive study about colitis in general. They are aware of the present need of a careful definition of ulcerative colitis, in particular. They suggest the following, adopted by the convention at Plombières, in 1935: Ulcerative colitis is a serious disease, involving the whole colon or only one of its segment, always spreading to its



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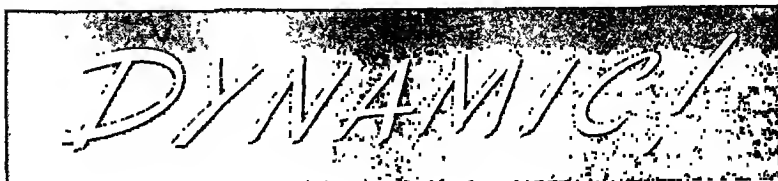
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surface and its distal end, revealing itself most of the time by an acute or chronic dysenteric syndrome, with periodic recurrence, and of unknown etiology. The periodicity of ulcerative colitis has attracted the attention of many authors who have stressed the similarity of such an evolution with the usual course of the gastro-duodenal ulcer. The diagnosis requires a complete examination of the feces, barium enemas, and proctosigmoidoscopy whose findings are essentials in distinguishing the ulcerative colitis from any other similar colonic ailment. Treatment is deceiving. The so-called specific therapy can boast of certain interesting results but has failed, so far, to prove its worth in the majority of cases. The same thing can be said of the therapy against local or focal infections. Local treatment, consisting of rectal dressings with Vitamin A, has given better results than the same procedures carried on with any antiseptic enrobed in a mucilaginous substance. Autohemotherapy and blood transfusion may be credited with a few decisive cures. Surgical indications are also clearly defined and explained. *Lymphogranuloma venereum of the ano-rectal region.* After a lengthy discussion of the similarity of the so-called rectal syphiloma described by Fournier in 1906, and the present rectal stricture, the writers point out the necessity of segregating the lymphogranuloma venereum of the rectum from other venereal diseases which it simulates in its local manifestations. Dealing with 120 rectal strictures, and 80 rectitis they have found positive specific reaction in more than 90% of the cases. This average is much higher than the one shown in the same respect in favor of syphilis and gonorrhea. The extensive clinical study involves the ano-rectal implantation and their associated lesions, such as the perirectal fistula, abscess, inguinal buboe, and elephantiasis pudendorum. Specific diagnosis depends upon positive Frei reaction which must be followed from the second to the eighth day, done with two control-antigenes, brought from different sources, kept in cool storage and properly sterilized. *Treatment.* Diathermic dilatation is a most valuable method of handling the rectal stricture. Iodine, stibium and sodium salicylate are more or less successful in curbing the infection, and specific therapy encounters a serious obstacle in the scarcity of the antigen. Surgical therapy, which has been so far limited to palliative colostomies, may be more helpful in performing radical resection of localized rectal lesions unaltered by medical treatment.

Roger R. Dufresne, Montreal, Can.

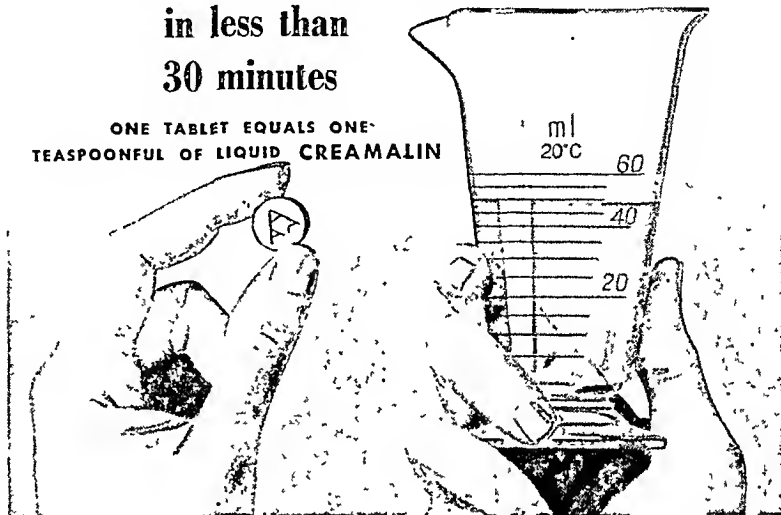
Sensible Dieting. By William Engel. New York, Alfred A. Knopf, 408 pp., 1939. Price \$2.50.

This is another of the many books now being put out with the idea of



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teaching people how to diet. It consists almost entirely of daily menus for different seasons of the year and for different fuel contents from 1,000 to 2,000 calories a day. This type of book might be very convenient, granting that the reader had first, a cook willing to prepare the meals according to the book, and second, a catholic taste for foods which would enable him or her to be satisfied with whatever was put on the table. We wonder how many persons would be willing or able to eat in such a prescribed way.

Engel lays claim to having started the lamb chop and pineapple diet in Hollywood. Actually some thirty years or so ago an old physician,

practicing near Santa Rosa in California, opened a little sanatorium where he fed every patient on meat and pineapple. He had a big vogue and doubtless helped a lot of men and women who had been overeating or who were sensitive allergically to one or more foods. Unfortunately for him, he tried to burn to death a girl with whom he had been living, and a prolonged vacation in the state prison somewhat injured his business.

The Doctor Prescribes Music. By Edward Podolsky, New York, Frederick A. Stokes, 134 pp., 1939. Price \$1.50.

From the time when David's singing brought relief to Saul in his jitters

spells, it has been known that music can have a good influence on many people. Here is a book in which there are actual detailed prescriptions of different types of music for different troubles. There are lists of titles of music that will thrill or soothe, that will drive away pain, or will help digestion.

It is a most interesting little book, and many will be glad to read it and to see what suggestions Dr. Podolsky makes. Some music-loving readers will doubtless disagree as to some of his choices. For instance, for wooing sleep, we can see how the New Waltz and the Largo from the New World Symphony might help but we wonder how well The Wedding of the Winds or Wotan's Farewell would go. We fear that Podolsky's last chapter on music and color contains a good deal of buncombe: what Dr. David Starr Jordan used to call Sciosophy, or the shadow of wisdom.

Biographies of Child Development. By A. Gesell, Catherine Amatruda, B. Castner and Helen Thompson, New York, Paul B. Hoeber, Inc., 328 pp. Price \$3.75.

The Yale Clinic of Child Development and its leader, Dr. Arnold Gesell, have long been known for pioneer work in this particular field. All of those who are interested in the problems of the mental development of infants and children will be interested in this book. Among the topics discussed in the several chapters are normal and retarded development, unusual command of words and ideas, fluctuating intelligence ratings, progressive acceleration and retardation of development rate, hemihypertrophy associated with mental defect, language problems, reading disabilities, irregularities in early mental development, immaturity and prematurity, endocrine gland deviation, effect of twinning, physical complications affecting mental growth, foster care and adoption, etc.

Medical Climatology. Climatic and Weather Influences in Health and Disease. By Clarence A. Mills, Springfield, Illinois. Charles C. Thomas, 296 pp., 1939. Price \$4.50.

This is a most interesting book and one that every physician can read with pleasure and profit. Whenever someone takes the trouble to correlate the curves showing the incidence of various diseases with changes in the weather, he is likely to find some very curious things. Some of them are so curious and so startling that the reader is inclined to wonder if he isn't reading a book by Baron Munchausen.

Actually, every layman and physician knows that the incidence of colds and pneumonia rises markedly

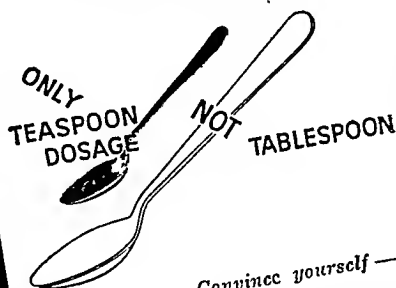
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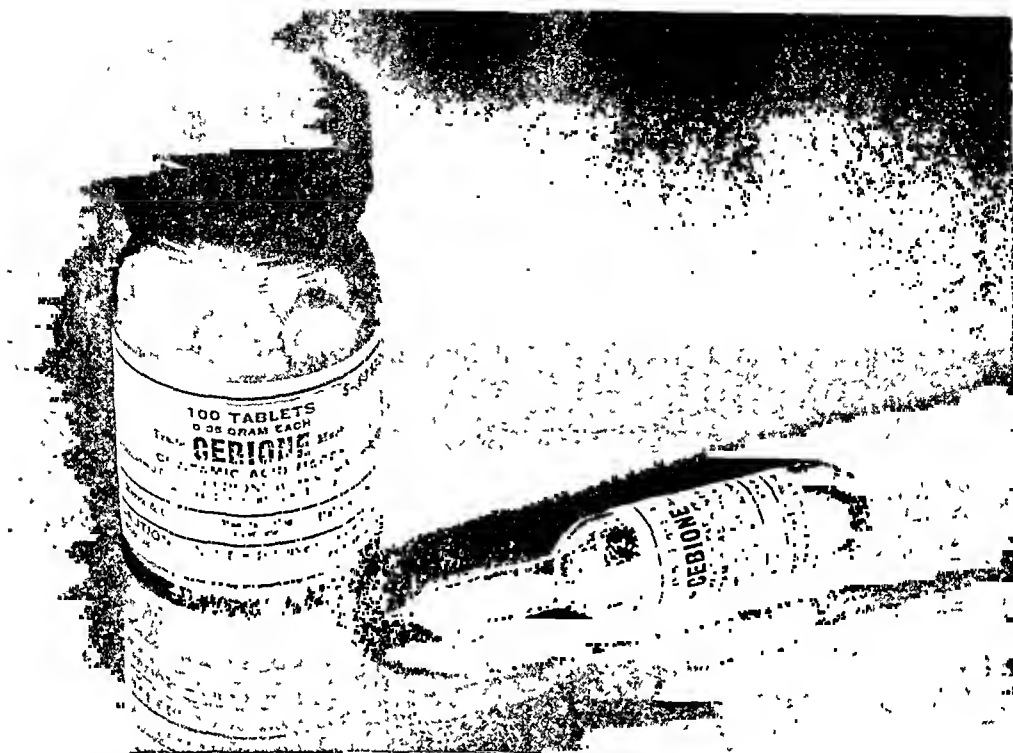
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and drops off again as summer comes, during the cold months of the year. Everyone knows that the joints of some arthritics tend to ache particularly badly the day before a storm comes. Everyone can see why the number of suicides in a large city might go up on a dull, dark day. One can see also how the incidence of rheumatic fever might vary with the weather, but it is curious to find Dr. Mills correlating weather with the incidence of dental caries, of deaths from coronary occlusion, and with the incidence leprosy, diabetes and goiter.

Very curious is the relation of the curve showing the incidence of conceptions each month with the curve

showing mean temperature. In Montreal people apparently get friskier in the summer, so that the number of conceptions then increases markedly, whereas in Charleston, North Carolina, where it is hot in the summer, the incidence of conceptions falls way off.

One can easily see, of course, why the incidence of attacks of angina pectoris should be highest in the winter, because walking against a cold wind is very difficult for men with a narrow coronary artery. In Cincinnati the curve showing the incidence of heart failure of all types is a mirror image of the curve repre-

senting mean temperature. In other words, heart failures come with the cold weather.

Most interesting to physicians will be Dr. Mills' chapter on the lessened incidence of disease of certain types in the southwest states where the changes of weather are not so violent as they are in the northern states. There not only the arthritic and the patient with pulmonary tuberculosis get better, but the patient with heart disease and diabetes is likely to be spared many trying ups and downs.

The reviewer has gotten more satisfaction from Dr. Mills' book than he has from those of some other writers. It has always seemed to him that any writer on this subject should have always at his elbow some hard-boiled, well trained statistician to be reminding him constantly that there might be some other explanation for the coincidence of two curves, or that the tremendous incidence of tuberculosis in Southern California, Colorado, and the Southwest is due to the fact that people with tuberculosis go there from all over the country.

We still think it would be an excellent idea if writers on this type of subject would, in the future, collaborate always with a statistician who would add a note to each table and graph saying whether or not he was satisfied with the data and the argument, and if he was not satisfied, show the author and reader where the loopholes might be. The reader would then be less inclined to put the book down with the feeling that it would be mighty interesting if it were all true.

Abstracts

Histopathologic Changes in the Nervous System in Cases of Peptic Ulcer. Archives of Neurology and Psychiatry, 41:871-912, May, 1939.

A. R. Vonderahe (University of Cincinnati) classifies the theories of the etiology of peptic ulcer as follows: 1—*non-neurogenic theories* which include the role of (a) secretory abnormalities, (b) vascular lesions, (c) bacteria and other parasites, (d) disturbances of internal secretion, (e) cytotoxins, (f) ferments and (g) local chemical and mechanical factors; 2—*psychogenic theories*, and 3—*neurogenic theories*. The literature is extensively surveyed and a new classification of neurogenic theories is arranged according to anatomic levels and based on both physiological and clinical observations. The evidence is presented for the association of peptic ulcer with lesions of (a) the cerebrium (pre-motor area), (b) diencephalon, (c) vagal and sympathetic nuclei and their peripheral nerves and ganglia,



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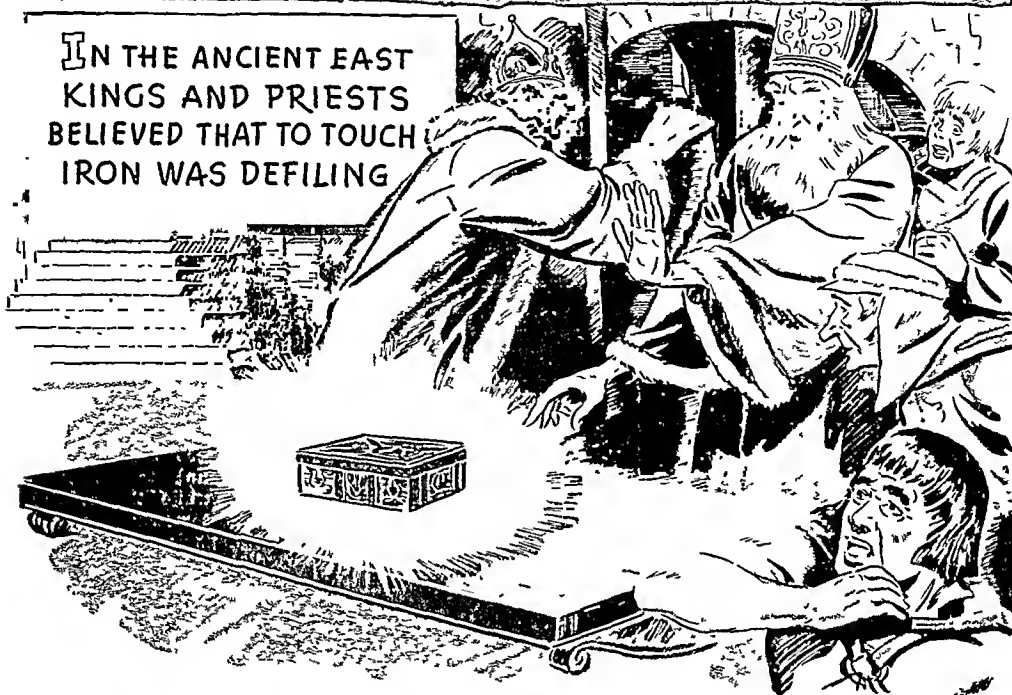
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and (d) the plexuses of Auerbach and Meissner and their local nerve terminations.

The author next describes fourteen cases of peptic ulcer, which presented at autopsy no evidence of grossly localized pathologic involvement of the brain. The diencephalon and adjacent structures were examined microscopically in all cases; in four cases, in addition to the diencephalon, the medulla, pons, mid-brain, frontal, precentral, occipital, temporal and hippocampal cortex were examined; in seven cases, in addition to the diencephalon, the medulla, pons and midbrain were examined, and in one

case, in addition to the above areas, the vagus and sympathetic nerves, the thoracic spinal cord, the coeliac plexus, the plexuses of Auerbach and Meissner and the nerve terminals in the ulcer area itself were studied. All material was fixed in formalin, embedded in celloidin, sectioned serially, and stained with Morgan's iron hematoxylin; in many instances supplementary stains were used.

Multiple hemorrhages appeared in the anterior hypothalamus at the level of the hypothalamic sulcus in the gray matter of the third ventricle between the fornix and the ependyma and implicated and superior portion

of the nucleus paraventricularis and cells of the substantia grisea. In some instances capillary hemorrhages involving the nucleus supraopticus and nucleus tubero-mammillaris also occurred. The cells of these nuclei showed varying degrees of acute retrograde change. In the thalamus, cells of the nucleus reuniens complex were implicated in hemorrhage; in some instances the nucleus paramedianus was also involved.

In the medulla multiple hemorrhages appeared in the dorsal motor nucleus of the vagus usually on both sides but with more intensity on one side. The level of the hemorrhage corresponded to that portion of the dorsal motor nucleus, which, according to Molhant, innervates the stomach and upper part of the small intestines. The hemorrhages were caudal enough to involve some of the cells of the nucleus cardiacus n. vagi (Malone). Aside from cells directly destroyed by hemorrhage, cells of the nucleus sympathicus n. vagi, (Jacobsohn) tended to resist toxic change while the cardiac cells appeared somewhat more susceptible. The hypoglossal nucleus, lying immediately adjacent to the dorsal motor nucleus presented in all instances a normal appearance. No hemorrhage was found in any other portion of the medulla save in the dorsal motor nucleus. Retrograde changes occurred in the nucleus tractus solitarius and in the nucleus of the descending root of the trigeminal. Retrograde changes were frequently noted in the cells of the inferior olive, while the cells of the phylogenetically older medial accessory olivary nucleus often presented a normal appearance.

In some cases of ulcer of many years duration, in addition to fresh hemorrhage, there was noted in the characteristic areas clusters of pale staining blood cells, deposits of hemosiderin, phagocytic cells with ingested hemosiderin and nests of proliferated glial cells. These findings suggest that hemorrhage occurred at various times in the course of the disease, and that various stages of healing were present.

Histologic examination of the pre-motor cortex and other cortical areas, the striatum, cerebellum, mid-brain and pons presented no finding which could be confidently interpreted as a causative factor in the production of chronic peptic ulcer. Acute retrograde changes in some of the cell groups occurred.

The sympathetic cells in the inter-medio-lateral gray column of the spinal cord, the peripheral vagus and sympathetic nerves and the coeliac plexus presented no abnormality. In the region of the ulcer itself, shrinking of the cell bodies of the plexuses

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Bullington, Smith, E. and
Felling, A.: Modern Medical
Treatment, Wm. W. & Co.,
New York, 1934, p. 271.



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of Auerbach and Meissner, perineuritis, and proliferation of the nerve filaments were observed, confirming the findings of other observers; these findings are regarded as secondary to the ulcer and the result of local irritation and inflammation.

A study of the diencephalon in thirty-five control cases indicated that hemorrhage may occur in the thalamus and hypothalamus in cases of severe irritative visceral diseases in the abdominal cavity and in occasional cases of diabetes mellitus. In fifteen of the control cases no hemorrhage occurred in the thalamus or hypothalamus; this series included

examples of asphyxia, cardiac failure and diabetic acidosis. In another group of control cases hemorrhage was noted as a result of brain trauma, massive lesions of the brain and severe obstruction of venous drainage. It was observed that in unilateral lesions, hemorrhage in this area tended to be bilateral. A study of the medulla in eighteen control cases revealed no evidence of any hemorrhages in the dorsal motor nucleus of the vagus or elsewhere in the medulla, suggesting that the presence of such lesions in cases of peptic ulcer is a fairly characteristic phenomenon.

The hypothesis is advanced that three factors enter into the production of these localized hemorrhages into the nucleus reuniens complex of the thalamus, the anterior part of the hypothalamus and the dorsal motor nucleus: (1) the effects on the cerebral vessels of alteration of the vascular bed in the splanchnic field especially noteworthy in any disease of the abdominal viscera, (2) the effects of anoxemia, vitamin deficiency, and other chemical factors on the cerebral blood vessels and (3) vasodilatory effects called forth by heightened functional activity in the anterior part of the hypothalamus, the nucleus reuniens complex of the thalamus, and dorsal motor nucleus of the vagus. The first two factors might be expected to act more diffusely and to explain congestion, perivascular edema and acute retrograde cell changes in many portions of the nervous system, while the third factor offers a basis for intense local vascular reaction such as is noted in all the cases of peptic ulcer presented here. This latter factor introduces into neuropathologic study mechanisms of the greatest importance clinically, namely, afferent stimuli.

In twenty cases of brain tumor with complete autopsy, four or 20 per cent presented ulceration of the stomach. Three of the tumors were of pituitary origin and one was in the fronto-parietal lobe. Three of the ulcers were of the acute type and one was of the chronic type.

In fifty-one cases of peptic ulcer with complete autopsies, twelve or 23.5 per cent were associated with gross brain lesions other than brain tumor, or with severe disease of the membranes. Chronic ulcers tended to be associated with chronic pathologic states of the nervous system and more acute ulcers with more acute disorders of the nervous system.

The evidence presented by the association of brain tumor and of the other gross lesions of the brain and its membranes with ulceration of the stomach and duodenum, as well as the imposing evidence presented by experimental studies, indicates that in many instances gastric and duodenal ulceration is caused by pathologic alterations in the nervous system. The possibility of a psychogenic origin or a non-neurogenic origin of some cases of peptic ulcer is not disproved by the result of this study.

Thus, while in some instances of peptic ulcer the role of the nervous system may be efferent and causative of peptic ulcer, in all instances the role of the nervous system is afferent and the site of a characteristic involvement once a severe irritative lesion of the stomach or duodenum is established. By considering the

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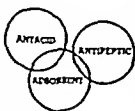
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nervous system in peptic ulcer in terms of the complete reflex cycle many of the characteristic symptoms and signs as well as sequelae find an explanation. Very striking indeed in many of these cases are the ascending pulse rates which become so rapid that counting is no longer possible; here capillary hemorrhage has occurred in the dorsal motor nucleus implicating the cardiac neurones, destroying their inhibitory effect and leaving the heart entirely to the accelerating effects of the sympathetic innervation. Most important of all, however, is the understanding of a probable reason for many of the

sequelae following recovery from a severe attack of peptic ulcer—the irritable pulse rate, the increased sweating, the signs of "sympathetic imbalance," all point to injury in the parasympathetic centers of the dorsal motor nucleus of the vagus, while quick fatigability, irritability, emotional changes, and alterations of metabolism, sleep and temperature regulation points to injury in the thalamus and hypothalamus. To regard such manifestations as merely neurotic is frequently untrue and injustice may be done by not recognizing an organic handicap.

TURELL, R., MARINO, A. W. M. AND NERB, L.

Observations Concerning Absorption of Sulfanilamide From Large Intestine in Man: An Experimental Study. The Brooklyn Hospital J., 1:90, April, 1939.

In a previous investigation, it was found that sulfanilamide introduced into the rectum of rabbits is rapidly absorbed. In the present communication the results of studies on the absorption of one per cent solution of sulfanilamide from the human colon and rectum are recorded. A series of eight normal individuals who received rectal instillations of one per cent solution of sulfanilamide showed the presence of the drug in the blood. In order to determine whether the drug is absorbed directly from the rectum or colon or whether it must pass to the ileum before being absorbed, the same investigation was repeated in a patient who three years previously had had an ileostomy with exclusion of the colon. It was demonstrated that absorption of sulfanilamide took place from the isolated colon. In another instance direct absorption of sulfanilamide from an isolated human rectal pouch was demonstrated. Sigmoidoscope studies revealed no apparent changes in the mucous membrane of the rectum and colon as a result of the rectal administration of sulfanilamide. The foregoing experimental studies showed that adequate concentrations of sulfanilamide can be maintained in the blood by means of rectal instillations of one per cent solution of sulfanilamide. The rectal route of administration is recommended when sulfanilamide cannot be given by mouth.

MARINO, A. W. M. AND TURELL, R.

Treatment of Internal Hemorrhoids by Injection: A Study Based on Observations of 5000 Injections. The Brooklyn Hospital J., 1:93, April, 1939.

This study based on 5000 injections, showed that injectional therapy when used with discretion and applied to properly selected cases has a well deserved place in the therapeutics of hemorrhoids. It can be applied to about 40 per cent of all patients with uncomplicated internal piles.

The procedure should be restricted to the treatment of uncomplicated, soft, bleeding, and moderate sized prolapsing, but easily reducible piles. Injectional therapy induces an inflammatory reaction within the interstitial tissue of the hemorrhoidal mass, thereby causing an obliteration of its vessels by thrombosis, which is followed by fibrosis. We are now studying experimentally the various



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LITERATURE UPON REQUEST



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successive histologic changes involved, and the fate of the fibrosis.

The contraindications, dangers and the technic of injection are described in detail. Properly performed injections should not result in complications. When any occur they usually are attributed to errors in technic. The patients should be followed for one year or longer. In six per cent of the cases there was a definite recurrence of the internal hemorrhoids. Since injectational therapy does not remove the original etiologic factors responsible for the development of hemorrhoids, recurrence can hardly be considered a failure in those instances where the cause was not eliminated.

Comparative studies show that hemorrhoidectomy is still the method of choice. In certain instances where hospitalization is undesirable or when hemorrhoidectomy cannot or should not be performed, injectational therapy may be elected. Injectational therapy was employed with satisfaction in diabetes mellitus, diabetes insipidus, pulmonary tuberculosis, neurosyphilis, and in patients with hypertensive cardiovascular disease with good myocardial compensation.

Injectational therapy may be employed with good chances of success in patients who have mild obstructive lesions of the vesical neck. When the lesion at the bladder neck is progressive in nature, this procedure fails to

relieve bleeding from uncomplicated internal hemorrhoids. In these cases hemorrhoidectomy is also unsuccessful unless the obstructive lesion at the vesical neck is first eliminated. After the enucleation or transurethral resection of the prostate, the edema in this region disappears, and the hemorrhoids, in most instances will regress.

Injectational therapy is useful in the early months of gestation. Urea and quinine hydrochloride should not be employed for obvious reasons.

The method of treatment of hemorrhoids by injection is not without danger. Surgical judgment as well as skill are essential, for although the method seems simple, unless one understands the rationale and technic, disappointment and complications may result.

NERN, L., TURELL, R. AND MARINO, A. W. M.

Absorption of Sulfanilamide from Rectum and Colon of Rabbits. The Brooklyn Hospital J., 1:88, April, 1939.

Sulfanilamide administered to rabbits by rectum in the form of solution, suppository or capsules is absorbed rapidly. The rabbits were found to be unsatisfactory animals for this experiment because they frequently expelled all or parts of the chemical. In spite of these difficulties, various amounts of sulfanilamide were found in the blood. The concentration of sulfanilamide in the blood stream was found to be the same in two rabbits when equivalent amounts were first administered orally, and in three days rectally. The possibilities that following rectal administration, the drug may be propelled to the ileum and absorbed from there were considered.

Robert Turell.

RABINOWITCH, I. M. AND FOWLER, A. F.

Variation of Weight of Dry Feces in Short Period Experiments with a Low Residue Neutral Ash Diet. J. Nutrition, 16(6):565-569, 1938.

The average daily weight of dried feces of normal individuals on ordinary diets, fluctuated widely, between 25 and 60 gm. per day. Over long periods on a diet constant composition, the average weight of the dried feces fluctuated within a much narrower range. In a series of 20 experiments, the average weight ranged within a few gms. only, even in short period experiments—3 to 20 days—providing the diet was low in residue and produced a neutral ash; the average excretion per day was 21.5 gm. with a standard deviation of 2.1



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METHODS FOR QUANTITATIVE ESTIMATION OF THE VITAMINS

1. The Determination of Vitamin D Activity

● About fifteen years ago it was clearly established that there could be present in certain foods or biological materials some substance which possessed antirachitic potency. Subsequently this "antirachitic factor" became known as vitamin D. Today, we know that at least ten sterol derivatives may exert antirachitic effects closely comparable to those of the originally discovered vitamin D (1).

Recognition of the existence of the antirachitic vitamin naturally stimulated investigation of methods whereby this dietary essential could be quantitatively estimated. Steady advances in knowledge of the causes and effects of rickets brought gradual improvements in these methods. Consequently, there are now available several techniques for the quantitative determination of vitamin D in foods or other biological materials.

The first and probably most widely employed method for estimation of vitamin D is by means of the so-called "line test" (2). In this technique as now employed (3), young rats are confined for 18 to 25 days to a diet conducive to development of rickets. These periods of time, with proper handling and confinement of the animals, are sufficient to induce a definitely rachitic condition. The rachitic rats are then properly grouped with respect to negative control groups to receive no supplements to the rachitic ration; positive control or reference groups to receive graded doses of some standard reference material; and "assay groups" to be given graded doses of the material under test. For the next 8 days the animals are fed daily doses of the proper supplement, either assay or reference material. No supplements are fed on the ninth and tenth days.

On the eleventh day the animals are sacrificed and either the proximal end of the tibia or the distal end of the radius or ulna dissected out, sectioned, cleaned and finally

immersed in silver nitrate solution. By double decomposition reaction, silver salts deposit where calcium is present in the metaphysis of the bone. When exposed to light these silver salts are reduced and form a dark line indicating the extent of calcium deposition. The experienced technician can estimate the degree of healing from rickets by the continuity and area of the line. By comparison of the results obtained on the various groups of animals, a quantitative expression of the antirachitic activity of the material under assay may be obtained.

A second method for evaluating vitamin D activity is that involving determination of "bone ash" (4). In this technique, final estimation of the degree of bone calcification—and thus the antirachitic potency of the substance under assay—is made by chemical analysis of specific bones of the experimental animals. A third assay method (5) is that involving roentgenological examination of certain bones. Comparisons of the bone densities of the various experimental animals serve as a basis for estimating the degree of healing from—or prevention of—rickets and hence permit determination of the vitamin D activity of the material under test.

Common foods as they naturally occur can hardly be considered as food sources of vitamin D. However, as exceptions, certain foods of marine origin (6) might be mentioned which consistently contribute small but definite amounts of the antirachitic factor to the diet. In addition, development of various means of fortifying foods with vitamin D—particularly those foods of importance in infant and child feeding—has made available other food sources of the vitamin (7). Among the many varieties of commercially canned foods will be found products of both types, which, when properly used or supplemented, should prove of value in obtaining an adequate intake of vitamin D, particularly by infants and children.

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- (1) 1938 J Am Med Assoc 110, 2150.
- (2) 1922 J Biol Chem 51, 41
- (3) 1936 The Pharmacopoeia of the United States of America, Eleventh Decennial Revision, 482

- (4) 1923 J Biol Chem 58, 71
- 1924 Ibid 61, 405
- (5) 1928 Biochem J 22, 135.
- (6) 1938 J Am Med Assoc 111, 528.
- (7) 1937 J Am Med Assoc 108, 206.

We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles. This is the fifty-second in a series, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research.



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and a probable error of the mean of 0.31.—Author (courtesy of Biological Abstracts).

NEDELL, A. J.

Experimental Gastric Ulcer (Peptic Episodes). Arch. Path., 26(5):988-1008, 1938.

Pitressin injections readily produce gastric and duodenal ulcers in experimental animals (dogs) and these are located in places common to the same lesions in man. The direct observations of the mucosa, together with the histological observations of the progression of ulcer formation from the very beginning to the end states,

definitely reveal the role of vascular dysfunction in ulcer formation. The vascular interference in local nutrition is the primary factor of these pathological developments. Depending on the constitutional type, on vascular instability and on the endocrine balance, on seasonal variation, on emotional situations, trauma, and meteorological factors, vascular incoordination may evidently be of sufficient intensity of duration to lead to prolonged local anoxia with resulting development of gastric and duodenal ulcers. Peptic ulcers should therefore be regarded as a local expression of vascular dysfunction inherent in con-

stitutional types unable to withstand the demands of the organism for adjustment to unusual environmental situations.—A. J. N. (courtesy of Biological Abstracts).

ALSTED, G.

On the Increasing Frequency of Gastro-Intestinal Hemorrhages. Acta Med. Scand. Suppl., 89, 332-336, 1 fig., 1938.

Dyspeptic disorders show increasing frequency among males, with increasing severity, and tendency to gastro-intestinal hemorrhage.—J. F. W. (courtesy of Biological Abstracts).

ASCHAM, LEAH, SPEARS, MARY AND MADDOX, DOROTHY.

The Availability of Iron in Various Foods. J. Nutrition., 16(5):425-436, 1938.

The ability of certain foods to promote Hb regeneration in young rats rendered anemic by prolonged feeding on whole milk was studied in order to measure the availability of the Fe in these foods. Canned collards and turnip greens induced greater rises in Hb when both the leaves and liquid were fed than did the dried forms of these greens. The Fe in canned turnip green leaves alone was less available than that in the dried leaves. The various dried foods studied fell into the following descending order: blackeyed peas and spinach, turnip greens and kale, collards and mustard, head lettuce, and lastly tendergreen and leaf lettuce. For these foods no relation was found between their available Fe content determined by bioassay and their ionizable Fe content determined chemically by the α, α' dipyrrolyl method.—(Courtesy Biol. Abst.).

SANSUM, W. D.

The Favorable Influence of Adequate (Higher) Carbohydrate and Lower Fat Diets on the Arteriosclerosis Problem Associated with Diabetes Mellitus. Acta Med. Scand. Suppl., 90:89-86, 1938.

Higher carbohydrate, lower fat diets, restored diabetic patients to a more normal state of health, and apparently lowered the incidence of arteriosclerosis. The problem is far from settled but such diets are feasible and have many other advantages aside from their probable relation to arteriosclerosis.—J.F.W. (Courtesy Biol. Abst.).

RAHMAN, LINCOLN, RICHARDSON, HENRY B. AND RIPLEY, HERBERT S.

Anorexia Nervosa with Psychiatric Observations. Psychosomatic Med., Vol. 1, pp. 335-365, July, 1939.

The frequency with which anorexia nervosa is mistakenly diagnosed as

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Science calls the common banana "*Musa Sapientum*," which means "fruit of the Wise Men." According to ancient legend, the sages of India reposed in the shade of the banana plant and refreshed themselves with its luscious fruit.

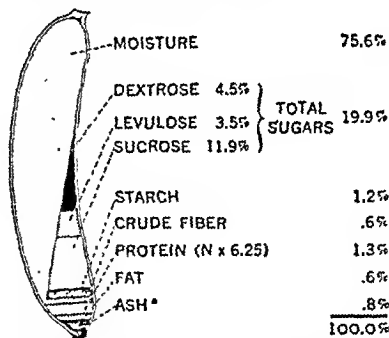
INTERESTING BANANA FACTS

THE ripe banana contains about 20% sugars with nearly 5% other solids consisting of protein, fat, pectins, minerals, vitamins and small amounts of starch and fiber. Its semi-solid texture must hence be attributed to the way in which moisture, sugars and the other constituents are held in a delicate meshwork of cellulose and pectin substances, and not to low moisture or high fat content. The sugars present are sucrose, levulose and dextrose. The two simple sugars account for about 40% of the total sugars.

The key to the varied usefulness of the banana is to be found in its composition. Special points stand out as qualifying it for inclusion in special types of diets. These are summarized in outline form below:

PROPERTIES OF RIPE BANANA PULP	MAKE IT OF VALUE IN
Readily assimilated sugars (along with vitamins, minerals and fiber).....	Infant Feeding
Caloric value (along with vitamins and minerals).....	Malnutrition
Satiety value and low fat (along with vitamins and minerals).....	Reducing Diets
Alkaline residue	Combating Acidosis
Vitamin content	Preventing Deficiency Diseases
Soft texture and blandness (with carbohydrates, vitamins, minerals, pectin and fiber).....	Intestinal Disturbances
	Normalizing Colonic Function
	Convalescent Diets

PROXIMATE COMPOSITION RIPE BANANA PULP



* Contains important minerals including calcium, copper, iron and phosphorus

VITAMINS IN BANANAS (Units per Ounce)
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LITERATURE ON REQUEST

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Simmonds' disease warrants reading this paper.

Characterizing this entity as a neurosis with psychosomatic manifestations, the authors present twelve patients. It is apparent that endocrine manifestations appear secondary to the starvation which the body undergoes. Obsessive, compulsive, anxiety, and depressive features are prominent.

The physical findings are those found in starvation, including "emaciation, dry, scaly skin, cold bluish extremities, amenorrhea, atrophic type of vaginal smear, subnormal temperature, slow pulse and low blood

pressure. Common personality characteristics were stubbornness, meticulousness, parsimony, ambitiousness, seclusiveness, shyness, dependence on others and difficulty in making friends. The patients' own statements indicated an avoidance of assuming normal sexual relationships. Frequently excessive interest by a parent in the function of the intestinal tract had been impressed on the patient in early life."

The major course of the treatment is regulation of regime plus psychotherapy.

H. H. Lerner, Boston, Mass.

THE AMERICAN PROCTOLOGIC SOCIETY

At its recent meeting in Brooklyn, Dr. Martin S. Kleckner, of Allentown, Pa., was elected President of the Society to succeed Dr. Dudley Smith of San Francisco.

The following other officers were elected:

Dr. Martin Marino, Brooklyn, Vice-President,

Dr. Frederick B. Campbell, Kansas City, Treasurer,

Dr. Cecil Gaston, Birmingham, and Dr. Walter Fansler, Minneapolis, Councillors,

Dr. Harry E. Bacon, Philadelphia, Editor,

Dr. Curtice Rosser, Dallas, Secretary.

The next annual meeting will be held in Richmond, Virginia, on June 9, 10 and 11, 1940, with Dr. E. H. Terrell as Chairman of Arrangements.

The following were elected to Fellowship:

Senior Fellows:

Dr. Alois Baehman Graham,

Dr. John Lemuel Jelks,

Dr. Collier Ford Martin.

Fellows:

Dr. Robert A. Searborough,

Dr. Warren W. Green,

Dr. Wm. K. McIntyre,

Dr. Jerrold P. Nesselrod.

Curtice Rosser, Sec'y.

CONDON, PALMER AND BURGESS, ALEXANDER M.

Clinical Experience with 95 to 98 Per Cent Oxygen in the Treatment of Abdominal Distention and Other Conditions. The New Eng. J. of Med., Vol. 221, pp. 299-302, Aug. 24, 1939.

The use of oxygen in the treatment of abdominal distention is reported in a series of forty cases. Twenty-five of the patients received definite benefit, five questionable benefit, and ten were uninfluenced. Cases with emphysema all had satisfactory results.

The method is considered life saving in severe abdominal distention such as is seen in pneumonia, typhoid fever, and post-operative peritonitis.

H. H. Lerner, Boston, Mass.

MCCANCE, R. A., WIDDOWSON, E. M. AND VERDON-ROE, C. M.

A Study of English Diets by the Individual Method. III. Pregnant Women at Different Economic Levels. J. Hyg., 38(5): 596-622, 1938.

Different economic levels did not affect the diets of 120 subjects in respect to the intake of caloric, fat and carbohydrate, whereas the intakes of protein, animal protein, Ca, P, Fe and Vitamin B rose convinc-



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Decholin and Decholin sodium have proved of value as choleretics in the treatment of chronic cholecystitis, hepatitis of toxic origin, non-calculous cholangitis, biliary engorgement, hepatic insufficiency, biliary dyskinesia, pre- and post-operatively in biliary tract surgery, and as diuretics in ascites associated with hepatic engorgement. (Contraindicated only in mechanical obstruction of the bile passages).

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"Proceedings of the Society for Experimental Biology and Medicine", 40:157, 1939.

Knox Gelatine is high in certain amino acids, which are precursors of muscular creatine. Thus, by increasing the phosphocreatine content of the muscle, Knox Gelatine increases its chemical store of potential energy.

The gelatine used in this study was plain Knox Gelatine (U.S.P.) which assays 85% protein and which should not be confused either with inferior grades of gelatine or with sugar-laden dessert powders, for these latter products will not achieve the desired effects. When you desire pure U.S.P. Gelatine, be sure to specify KNOX. Your hospital can get it on order.

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Empty one envelope of Knox Gelatine in a glass three-quarters filled with cold water or fruit juice (or half water and half fruit juice). Let the liquid absorb the gelatine. Then stir briskly and drink immediately before it thickens. Take four times a day for two weeks, then reduce to two envelopes a day. (May be taken before or after meals).

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ingly with income. A rise in spending power led to increased consumption of milk, fruit, vegetables and meat, and to a decreased consumption of bread and total cereals. Women taking the better diets were, on the average, significantly taller and less anaemic than those on the poorer diets. A comparison of the diets of the well-to-do women with the dietary requirements suggested by the League of Nations and other authorities suggests that the calorie standard has been set too high. The intake of Ca was suboptimal throughout and the diets of the poorer women were deficient in many

respects. — C.M.D. (Courtesy Biol. Abst.).

GOORLEY, J. T. AND LEE, C. O.

A Study of Enteric Coatings. J. Am. Pharm. Assoc., 27(5):379-384, 1938.

The following materials were used in coating capsules: keratin; salol; stearic acid; combinations of stearic acid with salol, paraffin, wax, ceresin, glycoesterin, lauric acid, palmitic acid, myristic acid; sandarac; shellac; collodion; tolu; benzoin; lacquers; albuminoids; waxes; formaldehyde-gelatin; castor oil; shellac, and aleo-

hol mixture. Of these studied, only the last-named gave evidence of disintegrating in the intestine within a reasonable time and of not being damaged by passing through the stomach. Best results followed administration on an empty stomach about 1 to 2 hours before meals. Successful enteric coatings must possess other properties than solubility simply in alkaline media. Small capsules appear to pass out of the stomach much more uniformly and within a shorter period of time than do larger capsules. — G.M.H. (Courtesy Biol. Abst.).

ANSON, M. L.

The Estimation of Pepsin, Trypsin, Papain and Cathepsin with Hemoglobin. J. Gen. Physiol., 22(1):79-91, 4 figs., 1938.

The procedures were completely described and the activity units defined. Directions for constructing a curve relating activity units to color values of digestion products were given.—E. S. (Courtesy Biol. Abst.).

BEST, C. H. AND RIDOUT, JESSIE H.

Under Nutrition and Liver Fat. J. Physiol., 94(1):47-66, 4 figs., 1938.

Many expts. on large groups of rats indicate that accumulation of fat in the liver during fasting is an extremely variable phenomenon; under the conditions of these expts., male rats usually do not exhibit an increase in total liver fat although there may be a slight rise in the %, while large female rats usually exhibit some increase.—T. C. B. (Courtesy Biol. Abst.).

FRANKLIN, D. J. AND MAHER-LOUGHNAN, G. P.

The "Circular" Musculature of the Small Intestine. J. Physiol., 94(3):426-429, 1938.

Experimental evidence is given, which supports Carey's view that there is a close spiral arrangement of muscular fibres in the small intestine of certain spp. The direction of the spiral is anti-clockwise, viewed from above (stomach end of the intestine). The physiological implications are discussed.—T. C. B. (courtesy of Biological Abstracts).

BORST, J. G. G.

The Cause of Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage From Peptic Ulcer. Acta Med. Scand., 97(1/2):68-88, 1938.

The hyperazotemia following massive gastro-intestinal hemorrhage depends on the increased formation of urea from the blood in the bowel. The hyperazotemia leads to relative poly-

PROCHOLON

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BEST,¹ in a study of biliary disease, found that much of the postoperative distress after gall-bladder removal was due to (a) spasm of the choledochal sphincter and (b) mechanical obstruction due to "remaining stone, mucous plug, inspissated bile, or blood clot." Both conditions resulted in a back pressure of bile throughout the intricate duct system within the liver.

To combat this problem, hydrocholeretics were used as part of a course of treatment designed to relax the sphincter area and at the same time to increase the bile flow and intraductal bile pressure in order to force the passage of the above-mentioned foreign bodies through the sphincter. Indicative of the value of the treatment is the fact that this regimen was established "as a routine part" of "post-operative management of all cases of gall-bladder surgery."

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¹ Best, R. Russell: *Rocky Mtn. M. J.* 36:319 (May) 1939.

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uria, and the urea concentration (45-60 g. per l) remains maximal until the blood volume is restored. If shock develops, both diuresis and maximum urea concentration fall and the blood urea rises further. The urea clearance may be the best measure of the severity of the shock. Post-hemorrhagic blood dilution is retarded by high diuresis, with a restricted fluid intake, by low blood albumin, and capillary damage. While post-hemorrhagic dilution is progressing, the kidneys excrete neither Na nor chlorides; if NaCl is given the plasma NaCl increases above the normal. The retention of salt and increased excretion of K form part of a regulating mechanism for restoring the normal filling of the arterial system.—J. F. W. (courtesy of Biological Abstracts).

PATTERSON, CHARLES A., SMITH, ERMA AND HALE, H. B.

Food Intake and Gastro-Intestinal Motility in the Albino Rat During Chronic CO Asphyxia. Proc. Soc. Exp. Biol. and Med., 39(3):509-511, 1 fig., 1938.

Albino rats exposed daily for one hour to 0.34 per cent CO consumed 23 per cent less food during a period of about 2 months than their litter mate controls. If treated with CO immediately after eating a test meal, peristalsis was inhibited and the ingestion time increased about 22 per cent.—Authors (courtesy of Biological Abstracts).

BANKS, BENJAMIN M. AND BARRON, LOUIS E.

The Phenolphthalein Test in the Diagnosis of Gastro-Intestinal Disease. The New Eng. J. of Med., Vol. 221, pp. 296-299, Aug. 24, 1939.

Fifty-two patients with intrinsic lesions of the gastro-intestinal tract and a hundred and fifty-one controls were examined by a modification of the Woldman phenolphthalein test to determine the presence of defects in the mucosa of the intestinal tract.

One fourth of the cases with alimentary disease failed to give a positive test, while one-sixth of the control cases gave a false positive. The results therefore indicate a wide range of error for the test thus limiting its usefulness.

H. H. Lerner, Boston, Mass.

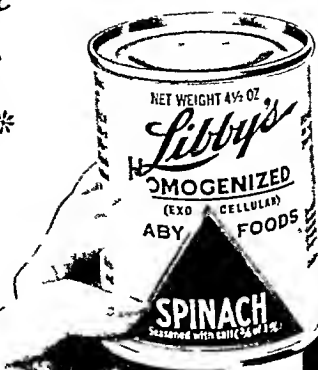
SEYMOUR, W. B., SPIES, TOM DOUGLAS AND PAYNE, WARREN.

The Gastric Secretion in Chronic Alcoholic Addiction. J. Clin. Invs., 18(1):15-18, 3 figs., 1939.

The gastric secretion in 40 chronic alcoholic addicts was studied, histamine being used as a secretory stimulant. There was no clinical evidence of vitamin deficiency, and no labora-

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— 1 minute



Homogenized
Vegetables
— 1 minute



Strained
Vegetables
— 37 minutes



Homogenized
Vegetables
— 36 minutes



Strained
Vegetables
— 62 minutes



Homogenized
Vegetables
— 61 minutes



Strained
Vegetables
— 154 minutes



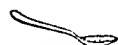
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Vegetables
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tory evidence of anemia. The results show an average diminished secretory volume and an average diminished acidity but the peptic activity of the gastric juice was apparently unimpaired. Comparison of the incidence of the achlorhydria with the expected normal incidence for the various age groups shows a considerable increase of achlorhydria over normal. Comparison of the incidence of achlorhydria in our series with a series of alcoholics with polyneuritis in which histamine was used as a secretory stimulant shows that the per cent with achlorhydria was much higher in the latter group.—W. B. S. (courtesy of Biological Abstracts).

STEWART, H. L. AND CANTAROW, A.

Experimental Carbon Tetrachloride Poisoning in the Cat. II. The Influence of Ligation of Single Bile Ducts. Arch. Path., 26(6):1121-1130, 1938.

In adult cats the subcutaneous injection of CCl₄ is followed by the development of characteristic regressive and regenerative phenomena in the central zones of the hepatic lobules. In cats subjected to ligation of single hepatic ducts 2 weeks prior to injection of CCl₄ the hepatotoxic effect of this poison is distinctly less marked than in previously normal animals. This difference is strikingly evident in both polygonal and Kupffer cells. Except at 2 and 8 days following injection, the regressive changes are of approximately equal severity in obstructed and nonobstructed lobules; at those stages the damage is distinctly more marked in the latter. The morphological differences between the 2 groups of animals are reflected in the functional activity. Abnormalities in bilirubinemia, retention of bromsulphalein and urobilinuria are less marked in those with ligation of single bile ducts than in previously normal animals. The possible causes of these differences are discussed.—A. C. (courtesy of Biological Abstracts).

MEULENGRACHT, E.

Histologic Investigation Into the Pyloric Gland Organ in Pernicious Anemia. Am. J. Med. Sci., 197(2):201-214, 6 figs., 1939.

In earlier works by the author it was shown that the antianemic factor of the stomach (Castle's intrinsic factor) must be secreted by the pyloric glands and the histologically identical Brunner's glands. Now stomach and duodenum from 8 pernicious anemia patients have been subjected to a histologic investigation. Gastritis changes in the fundus portion with atrophy of the glands and disappearance of parietal and



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REPRINTS of the Editorial "Aids to Normal Bowel Function." "Amer. J. Dig. Dis., March, 1939; J. A. Borgen, M.D., will be supplied on request.

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chief cells were found in all 8 cases. But the gastritic changes were less pronounced in the pyloric portion, and the glands seemed relatively well preserved; no histologic changes could be demonstrated in Brunner's glands. How the above finding, which at first sight is rather surprising, can be brought into line with the present conception of the pathogenesis of pernicious anemia is discussed.—E. M. (courtesy of Biological Abstracts).

AUER, JOHN AND SEAGER, LLOYD D.
Functional Activity of Pancreatic Ampulla in Rabbit. Proc. Soc. Exp. Biol. and Med., 39(3):542-543, 1938.

In rabbit under barbital narcosis, the intraven. inj. of a crude secretin mixture containing histamin causes a series of contractions and relaxations beginning at the junction of the pancreatic duct with the ampulla. The contractions gradually increase in strength and frequency until one sweeps over the entire ampulla. Each contraction is followed by a relaxation. A complete contraction may last 1-2 seconds. The relaxation generally proceeds from the distal end of the ampulla to the duct. The number of contractions may reach 10 per minute after one injection and they persist in decreasing numbers some 10 minutes. The same events may be seen in the bile papilla which in the rabbit is about 15 cm. distant from the pancreatic ampulla.—J. A. (courtesy of Biological Abstracts).

ELTON, NORMAN W.

The Relation of the Liver to Nutrition, with Special Reference to the Nervous System. II. Section on Clinical Pathology of the Liver. Rev. Gastroenterol., 5(2): 208-214, 1938.

A discussion of different liver function tests.—G. H. Chapman (courtesy of Biological Abstracts).

BINET, M. E.

Hepatic Insufficiency in Chronic Colitis. Rev. Gastroenterol., 5(3): 287-292, 1938.

Colitis frequently develops into biliary infection and hepatic insufficiency. The most serious sequel in malnutrition, often hepatic in origin. G. H. Chapman (courtesy of Biological Abstracts).

ALT, H. L., CHINN, H. AND FARMER, C. J.

The Blood Plasma Ascorbic Acid in Patients with Achlorhydria. Am. J. Med. Sci., 197(2):229-233, 1939.

Evidence in the literature suggests that achlorhydria might be a predis-

posing factor in the production of Vitamin C deficiency. Determinations of the reduced ascorbic acid content of the plasma were made in 44 patients with achlorhydria. This group consisted largely of patients with pernicious anemia or achlorhydric anemia in remission. The mean value of 0.57 ± 0.02 mg. ascorbic acid per 100 cc. plasma obtained in the achlorhydric patients was significantly lower than the mean value of 0.79 ± 0.03 mg. per 100 cc. obtained in 24 control cases. This difference was not related to variations in the diet. Various experiments suggest that anacidity and malabsorption may explain, in part at least, the low plasma ascorbic acid observed in the achlorhydric patients.—H. C. (courtesy of Biological Abstracts).

LOEW, E. R. AND PATTERSON, T. L.
The Reflex Influence of the Lower Portion of the Large Intestine on the Tonus and Movements of the Empty Stomach. Quart. J. Exp. Physiol., 28(4): 305-314, 3 figs., 1938.

Distention of an intrarectal balloon in gastric fistularized dogs produces inhibition of the tonus and motility of the empty stomach. Small amounts of pressure (6-18 mm. of Hg.) generally produce definite effects, the duration and degree of this inhibition being somewhat dependent on the magnitude of the intrarectal pressure. Recovery usually occurs even while the pressure is maintained in the rectum although this pressure may decrease when the rectum adapts itself. Dog's undiluted gall bladder bile produces similar effects when introduced into the rectum in such a manner that the animal is undisturbed during the administration. Glucose and physiological saline solutions are negative.—Authors (courtesy of Biological Abstracts).

STEWART, H. L. AND ANDERVONT, H. B.

Pathologic Observations on the Adenomatous Lesion of the Stomach in Mice of Strain 1. Arch. Path., 36(5):1009-1022, 1938.

A spontaneous adenomatous lesion in the pyloric chamber of the stomach in mice of strain 1 is described and illustrated. The lesion occurs in virtually all mice of both sexes of this strain and is the chief cause of death in mice of this strain. Mice of strain 1 are known to die at a relatively early age. The lesion is characterized by an adenomatous, hypertrophic, glandular overgrowth of the pyloric mucosa; degeneration and infiltration

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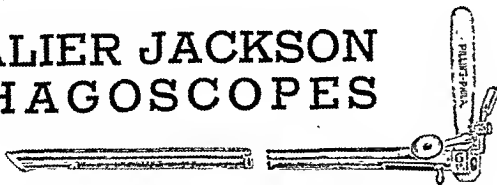
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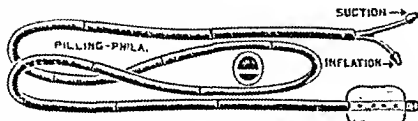
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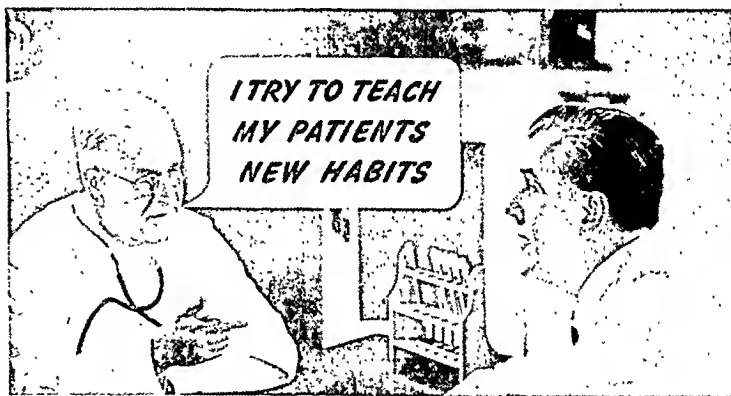
by inflammatory cells were present together with development of atypical epithelium with limited penetration into the deeper gastric wall and blood vessels. Although histologic studies reveal certain features that are somewhat suggestive of malignant growth, there are contradictory criteria, such as the symmetrical development of the process and the absence of metastases, unlimited local spread, extensive ulceration and destruction.—Authors (courtesy of Biological Abstracts).

HESLOP, T. S.

The Hypothalamus and Gastric Motility. Quart. J. Exp. Physiol., 28(4):335-340, 4 figs., 1938.

The hypothalamus was stimulated using Souttar machine for localization and Thyatron valve stimulator. Gastric motility was recorded by X-ray. Stimulation of supra-optic group of nuclei caused marked increase in rate and depth of peristalsis, tonic contraction of pyloric antrum and a very rapid passage of the barium paste into the intestine. Stimulation of mammillary group caused a momentary relaxation of the pyloric antrum only. Experiments were all carried out on 2½ kgm. female cats.—T. S. H. (courtesy of Biological Abstracts).

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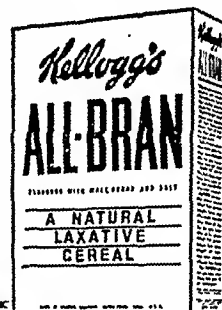
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Intubation Studies of the Human Small Intestine:

XVII. The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon*

By

KENDALL A. ELSOM, M.D.

and

J. L. DROSSNER, M.D.†

IN spite of the well established pharmacologic observation that atropine depresses the motor function of the bowel its clinical use for that purpose has often been disappointing. We have consequently taken advantage of the technique of intestinal intubation, as developed in this clinic (1), and as previously employed by Abbott and Pendergrass (2) in a study of morphine, to determine objectively the effects of atropine and belladonna on the motor functions of the small intestine and colon of man. Both drugs produced a marked and lasting decrease in tone and motor activity of whatever portion of the tract was studied.

METHODS AND SUBJECTS

As previously described (2) the apparatus was introduced under fluoroscopic guidance to any desired portion of the tract. The balloon was then inflated with approximately 40 cc. of air under 10-12 cm. of water pressure and connected with a spirometer type of volume recorder which activated a writing lever. In some instances a suspension of barium was introduced to permit simultaneous fluoroscopic observation of the calibre and motor activity of the bowel immediately proximal or distal to the inflated balloon. The method employed in these experiments has limitations discussed by Abbott (2). If the balloon enters a constricted portion of the gut, or is impinged upon by a bolus of intestinal contents the writing lever may indicate an increase in tone which is fictitious. Simultaneous fluoroscopic study usually discloses the fact, however, and therefore serves as a control of this part of the method. No technical errors now recognized produce an apparent fall in tone.

Except for 3 individuals who had abnormalities considered suitable for study all the subjects were without demonstrable gastro-intestinal disease. Two of the three showed small intestinal hypermotility and hyper-tonicity by roentgen examination and a third had ulcerative colitis for which an ileostomy had been performed. This latter subject provided an opportunity for simultaneous intubation through the ileostomy opening of the terminal ileum and the colon. In all subjects control tracings of intestinal activity were obtained before atropine sulphate was injected hypodermically. In a few instances atropine or belladonna was administered orally.

ACTION ON THE DUODENUM

Eight observations were made on 5 subjects. The control tracings from the normal duodenum have two

chief characteristics: The intestinal tone is high and the motor activity is great. Two types of waves are recorded as a rule, large peristaltic waves occurring every minute or two and lasting approximately a minute, on which are superimposed frequent small undulations produced by rhythmical contractions.

Administration of atropine sulphate was followed (Fig. 1) in 10 to 15 minutes by a gradual fall in intra-duodenal tone. The large peristaltic contractions were altered simultaneously, often becoming more pronounced as the tone decreased, then gradually diminishing in size and frequency and ultimately disappearing. The small rhythmical waves were decreased in size though usually not in frequency. This effect of atropine was fully developed within 20 minutes

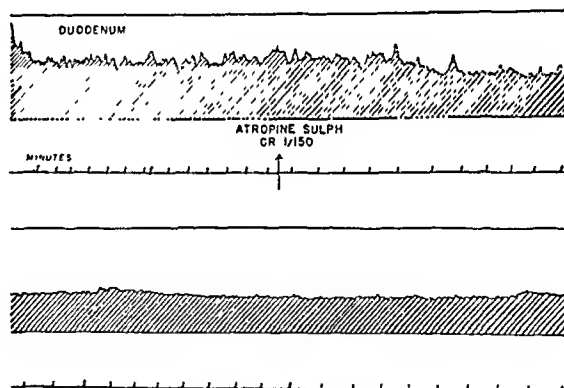


Fig. 1. The effect of atropine on the duodenum. In this and the following figures the upper horizontal line represents the position of the writing lever when the balloon is empty, the base line its position when the balloon contains 40 cc. of air. Time in minutes.

after the injection, and lasted for 1 to 2 hours. Recovery was gradual, with first an increase in size of the small undulations, then the appearance of peristaltic waves and finally an increase in tone.

ACTION ON THE JEJUNUM AND ILEUM

The results of 6 experiments on the jejunum and 3 on the ileum are here considered together since the tracings obtained from these portions of the bowel are similar to each other and rather different from those obtained from the duodenum. In the control tracings taken from these portions of the bowel the high tone and the marked motor activity which characterize the duodenum diminish progressively as the balloon descends into the more distal segments of the small bowel. The large, relatively infrequent peristaltic

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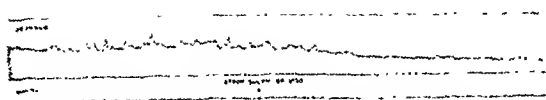


Fig. 2. The effect of atropine on the jejunum.

waves characteristic of the duodenum are inconspicuous in tracings from the jejunum. The small, rhythmic undulations are often the only evidence of motor activity. The effects on the jejunum and ileum produced by atropine were perhaps less striking than those on the duodenum but were no less definite. Fig. 2 shows a representative tracing obtained from the upper jejunum of a normal subject. The first detectable effect was a moderate decrease in intestinal tone. The character of the waves then gradually changed. The larger peristaltic waves decreased and ultimately disappeared, while the rhythmical contractions became smaller, but increased in frequency. The effect of atropine on the ileum in normal subject is seen in Fig. 3. In this instance a suspension of barium had been introduced proximal to the inflated balloon. This procedure altered the type of control record normally obtained from this section of the gut. Large con-



Fig. 3. The effect of atropine on the ileum.

traction waves on which small undulations were superimposed occurred every 1 or 2 minutes and lasted approximately 1 minute. The effect of atropine is clearly apparent. Ten minutes after its injection the tracing was a straight line, except for small, rapid rhythmical waves.

Fig. 4 shows a tracing from the jejunum of a patient, (Mrs. E. R.) whose case history is summarized below. It is abnormal in two respects: the tonus is higher than that customarily found in the jejunum, and the motor activity, with fairly large peristaltic waves, is unusually great. The effect of atropine (0.6 mg.) was striking. A decrease in tonus occurred within 10 minutes after the injection while the peristaltic waves were as large or larger than those in the control period. Within 20 minutes after the injection, the peristaltic waves were absent and the small undu-

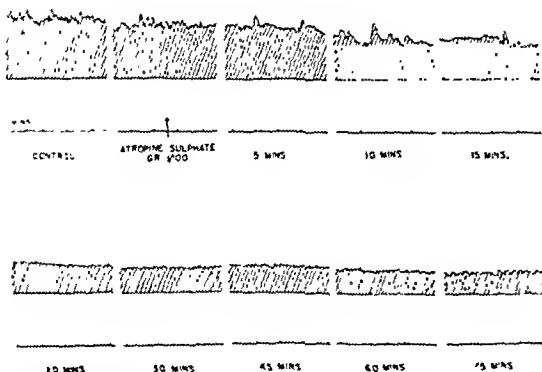


Fig. 4. The effect of atropine on the jejunum of a subject with small intestinal hypermotility and hyper-tonicity.

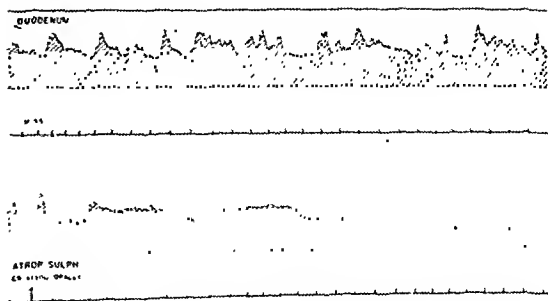


Fig. 5. The effect on the duodenum of atropine administered orally.

lations were greatly decreased in size. Seventy-five minutes after the injection the latter waves had increased in prominence, but peristalsis was still absent and the tonus was greatly diminished.

ACTION ON THE COLON

Four observations were made. In 2 normal subjects the effects were only slight, consisting in a decrease in tone and reduction in motor activity. In these two instances the colon was relatively inactive during the control period and interpretation of the effects of

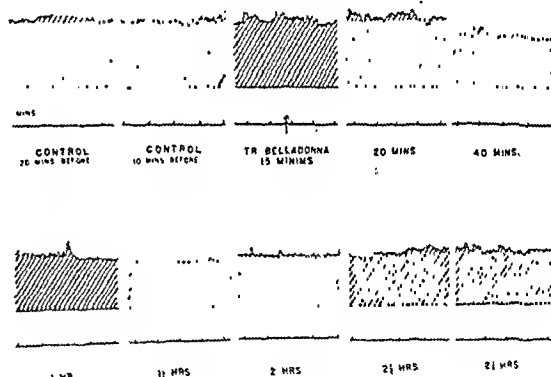


Fig. 6. The effect on the jejunum of Tr. Belladonna administered orally.

atropine was difficult. In the subject with ulcerative colitis the contractions of the colon were abnormally frequent and here the anti-spasmodic action of atropine was clearly apparent. Fig. 7 shows the record obtained from a patient with partial obstruction in the sigmoid region. The control tracing, obtained from the cecum, records frequent large contraction waves which expelled most of the air from the balloon. No such waves appeared after the administration of

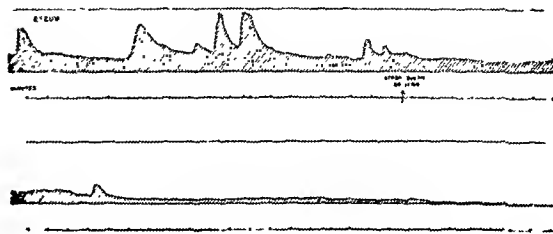


Fig. 7. The effect of atropine on the colon of a subject with partial colonic obstruction.

atropine (0.4 mg.) and the tonus was definitely diminished.

EFFECTS OF ORAL ADMINISTRATION

Atropine sulphate (Fig. 5) and tincture of belladonna (Fig. 6) orally administered produced effects qualitatively similar to those already described for hypodermic injection. The effects were slower in onset, appearing as late as 30 minutes after administration of the drug, and were less marked and less prolonged than from a similar dose administered subcutaneously.

DURATION OF ACTION

The decrease in the peristaltic and rhythmical contractions produced by 0.4 to 0.6 mgm. of atropine sulphate persisted as a rule for 1½ to 2 hours, with gradual return to normal. The effect on intestinal tone was more lasting. In Fig. 6 for example, the tone was still decreased 2 hours after administration of the drug although the contraction waves had returned to their normal size. Because of lack of time most of the observations had to be discontinued while the tone was still abnormally low.

THE EFFECT OF ATROPINE ON SMALL INTESTINAL MOTILITY

The marked decrease in motor activity observed in all portions of the intestine after atropine prompted a study of the rate of passage of the usual barium meal through the small bowel. It is generally agreed that atropine delays gastric emptying (3). Since the rate at which barium leaves the stomach in part determines the speed of its propulsion through the small intestine, the factor of gastric emptying was eliminated as follows: A normal subject was intubated with a Rehfuß tube, the tip of which was observed to lie

in the third portion of the duodenum. In an effort to simulate conditions of normal gastric emptying 175 cc. of a barium suspension were introduced into the duodenum in 7 divided doses of 25 cc. each, injected at 15 minute intervals. The rate of passage of the meal was carefully determined by frequent fluoroscopic examinations. One week later the procedure was repeated under identical conditions except that atropine sulphate (0.4 mgm.) was injected subcutaneously 10 minutes before the introduction of the barium, and 0.2 mgm. was injected 1 hour and 45 minutes following it. Table I indicates the observed differences in motility. The following observation of the effect of atropine in a patient with abnormally rapid small intestinal motility appears to be of practical value:

E. R. (No. 39-37, 955) a white woman, aged 50, complained of diarrhea of 12 years duration. She passed from 5 to 10 stools daily. Flatulence and mild abdominal pain often preceded the passage of the stools, which were liquid or semi-solid. Tenesmus was marked. She was a chronic invalid because of marked asthenia.

Physical examination was negative. Hemoglobin was 74 per cent (Sahli). Extensive laboratory tests were negative. Proctoscopic examination and repeated stool examinations revealed nothing of significance.

Gastro-intestinal roentgen examination disclosed a hypertonic small intestinal pattern with marked hypermotility. At a second examination 3 days later, atropine sulphate (0.4 mgm.) was administered hypodermically 7 minutes before the barium was swallowed, and the dose repeated in 2 hours. The resulting delay in gastric emptying time, the decreased small intestinal motility and the altered pattern are illustrated in Fig. 8.

Twenty drops of tincture of belladonna were administered therapeutically 3 times daily. The diarrhea immediately ceased, one or two formed stools being passed daily, and she stated that she had not felt so well for 10 years. For a two day period, when she was unable to obtain the drug, the diarrhea reappeared, only to disappear when medication was resumed.

DISCUSSION

The effects produced by atropine in the human small intestine and colon are definite. Under the conditions of our experiments the tone is lessened, the muscular contractions are diminished, and, as a result, intestinal motility is decreased. The results were uniform and dependable. In 21 observations the action was marked in 14, moderate in 8, slight in 1, and absent in only 1. These results are in general agreement with evidence derived from the small intestine of animals (4), and the stomach (5, 6) and colon (7) of man.

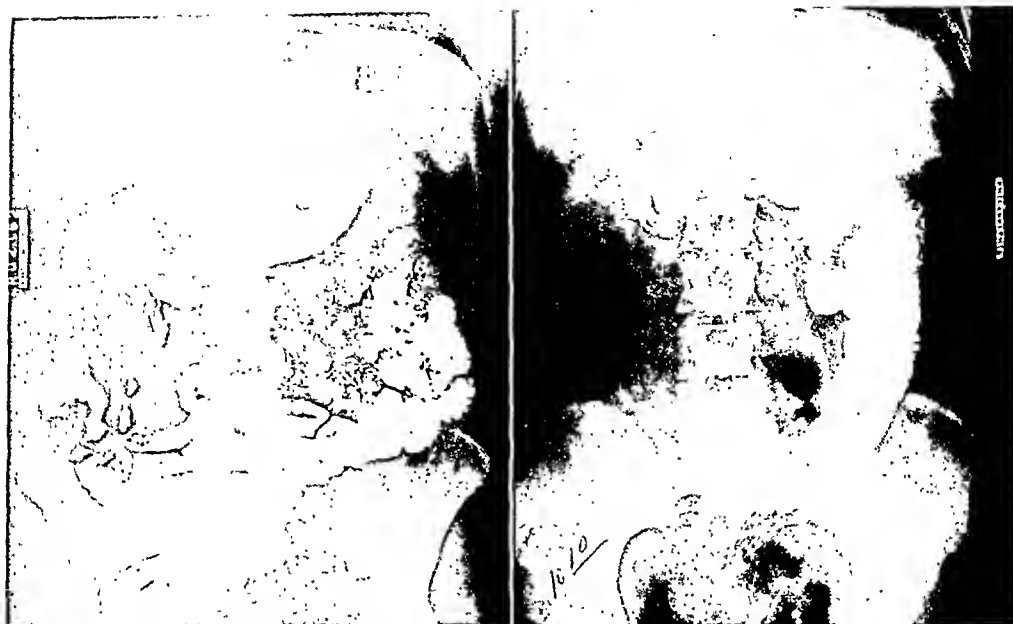
The statement of Cushny (8) that "small (therapeutic) doses of atropine appear to arrest only certain abnormal violent forms of contraction" has not been borne out in our experiments on man, since both abnormal contractions and those observed in the normal bowel were equally affected. The statement of Bastedo (9) that "in doses usually employed by mouth or permissible for any continued treatment, atropine and belladonna are practically without effect on the secretory and motor functions of the stomach" cannot be applied to the small intestine and colon.

While it is true that a balloon occluding the bowel creates an abnormal situation it is impossible to say whether it reproduces any observed clinical disturbances. This uncertainty, however, does not, in our opinion, invalidate the general conclusion that the ob-

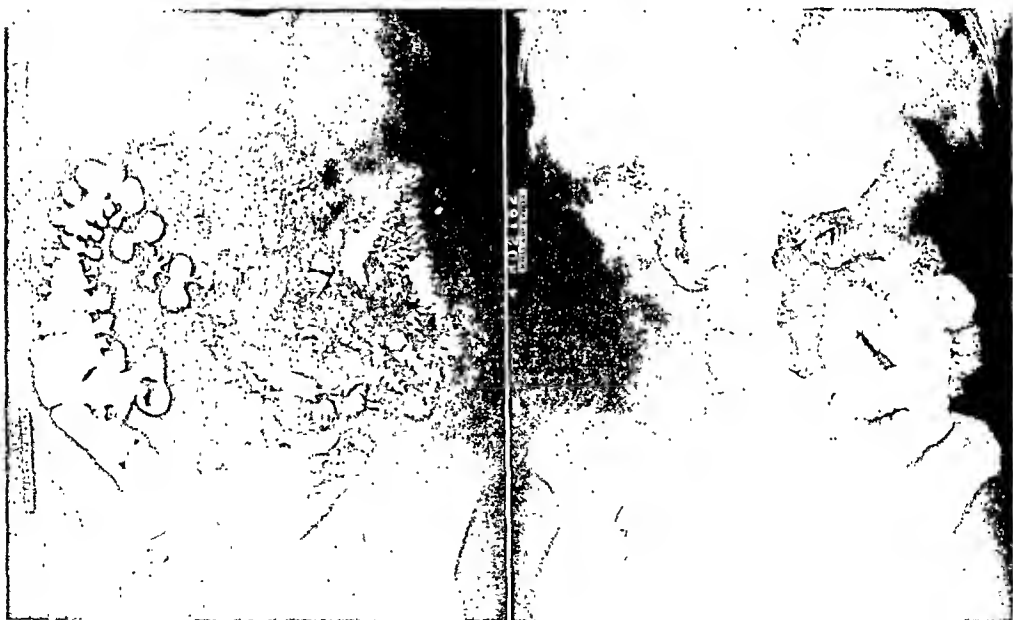
TABLE I

Small intestinal motility before and after the injection of 0.4 mgm. of atropine sulphate

Hours After Introduction of Barium Into Duodenum	The Position of the Barium Meal	
	Without Atropine 2/18/39	With Atropine 2/25/39
½	Chiefly in the upper jejunum.	Entire meal in first few inches of jejunum.
1	In ileal loops situated in pelvis and right lower abdominal quadrant.	Entire meal in duodenum and first two jejunal loops.
1½	Position of head of column not materially changed, most of the barium in mid-jejunum.	Head of the meal in distal jejunum. Most of barium in proximal jejunum.
2	No appreciable change in past half hour.	No appreciable change in the past half hour.
2¾	Head of meal at hepatic flexure of colon. Most of barium in terminal ileum. Observations discontinued.	No appreciable change.
3		No appreciable change.
4		Most of barium in proximal loops of ileum, none in loops situated in pelvis.
5		All of the barium now in the lower ileum, head of column just entering terminal ileum.
5½		Head of column has just reached the cecum.



A



B

served decrease in both tone and muscular activity of the intestinal tract produced by doses of atropine which are well tolerated can properly be expected to produce useful results.

CONCLUSIONS

Atropine sulphate and tincture of belladonna have been administered to normal subjects and patients

with gastro-intestinal disease and their effects on the small intestine and colon studied by means of intestinal intubation combined with fluoroscopy.

In therapeutic doses they produce definite and prolonged effects on the small bowel and colon consisting of a marked decrease in tone and in peristaltic activity and of a less striking effect on rhythmical contractions.



Fig. 8. The effect of atropine on small intestinal hypermotility and hypertonicity. Left hand column, before atropine. (a) 25, (b) 95 and (c) 145 minutes after a barium meal. Right hand column, after atropine. (a) 20, (b) 90 and (c) 120 minutes after a barium meal.

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XVIII. Intubation Studies of the Human Small Intestine: The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon*

By
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and
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IN the present study the technique of intestinal intubation has been utilized to determine the effects on the human small intestine and colon of pitressin and amphetamine (benzedrine) sulphate. Similar studies of morphine (1) and of atropine (2) have been re-

ported from this clinic. The method of intestinal intubation makes possible the objective demonstration of drug effects on portions of the intact human intestinal tract hitherto inaccessible, and permits evaluation in man rather than in laboratory animals of the uses and limitations of drugs.

Methods and Subjects

The method of intestinal intubation as developed and carried out in this clinic (3) requires no further description here. It permits the introduction to any

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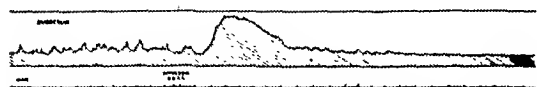


Fig. 1. The effect of pitressin on the duodenum of a normal subject. In this and the following figures the upper horizontal line represents the position of the writing lever when the balloon is empty, the base line its position when the balloon contains 40 cc. of air. Time in minutes.

portion of the intestinal tract of a balloon from which pressure changes may be recorded. A barium suspension introduced through the tube allows fluoroscopic observation of the bowel adjacent to the balloon. These two procedures complement each other, and with certain recognized limitations (1) constitute in our opinion a satisfactory method of study.

The subjects were without significant gastro-intestinal disease, except for one with ulcerative colitis in whom an ileostomy had been performed. In this subject the colon and terminal ileum were simultaneously intubated through the ileostomy opening. After suitable control observations the effects of pitressin or amphetamine were studied following hypodermic administration.

I. PITRESSIN

Effect on the Duodenum

The administration of 0.5 to 1.0 cc. of pitressin was followed in 2 to 6 minutes by a brief but marked spasm of the duodenum in 4 of 5 subjects. (Fig. 1). At this time fluoroscopic examination revealed a pronounced diminution in calibre of the duodenum which lasted 5 to 10 minutes and was accompanied by nausea and epigastric discomfort. Following this period of contraction relaxation of the duodenum occurred and persisted for 10 to 20 minutes; simultaneously duo-

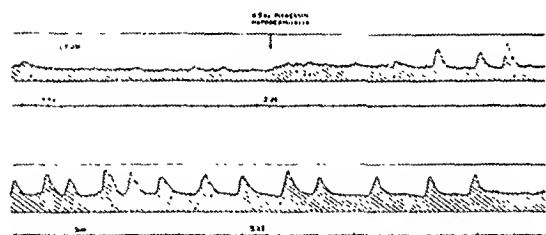


Fig. 2. The effect of pitressin on the ileum of a normal subject.

denal tone and peristalsis were reduced, and the subjective discomfort present during the period of contraction disappeared. The predominant effect of pitressin on the duodenum was, therefore, one of relaxation, since the initial period of contraction was relatively brief.

Effect on the Jejunum

The effect of pitressin on the jejunum was less definite than on other portions of the bowel. In none of 4 observations did 0.5 to 1.0 cc. of the drug produce striking results. Jejunal tone usually decreased slightly while peristalsis was increased. The small rhythmical waves consistently disappeared.

Effect on the Ileum

The administration of pitressin was followed by increased motor activity of the ileum in 12 observations

on 8 subjects. The evidence of this was of 5 types: (1) The pressure tracings often showed an increase in tone followed by the development of large peristaltic waves. (Fig. 2). (2) Fluoroscopic observation revealed hyperperistalsis, with rapid movement of barium from the terminal ileum into the cecum. This sometimes resulted from a peristaltic rush observed in the lower 18 inches of the ileum. The barium, in a continuous column before the administration of pitressin, was often divided into discrete segments, separated by narrow bands of contracted bowel. Peristaltic movement of the small bowel was visibly increased in most instances. (3) The tip of the tube, under the control conditions of our experiments, usually remained stationary once observations had begun. In several instances it advanced considerably during the



Fig. 3. Simultaneous tracings from the ileum and colon of a subject with an ileostomy for ulcerative colitis. The effect of pitressin.

action of pitressin. In one subject the forward advance of the tube had been stopped prior to giving pitressin by an acute kink of the ileum. After administration of the drug the tube traversed the angulation of the bowel without further delay. (4) In the subject with an ileostomy pitressin regularly increased the observable muscular activity of the exposed loop of ileum. (5) The amount and frequency of discharge of ileal contents in this subject were augmented after administration of the drug.

The activity of the ileum was modified by contractions of the colon produced by pitressin. Fig. 3 shows a record obtained by simultaneous intubation through an ileostomy of the terminal ileum and the colon. The first effect of the drug on the ileum was an increase in tone. During two spasmodic contractions of the colon the ileum was quiescent. This was evident both in the tracing and in the exposed bowel. As the colon relaxed increased ileal activity was resumed.

This reciprocal activity has also been observed fluoroscopically in normal individuals given pitressin. In one subject, with the tube in the terminal ileum, the outline of the gas-filled cecum was clearly visible. Following the administration of the drug rapid movement of barium through the terminal ileum occurred. The cecum and ascending colon dilated and remained quiescent during this period. The colon then contracted and the ileum became entirely inactive.

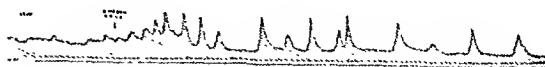


Fig. 4. The effect of pitressin on the ileum of a normal subject.

We have occasionally observed an effect on the ileum somewhat similar to that described in animals (4). (Fig. 4). Pitressin produced an initial increase in tone and an alteration in the character of the recorded waves. Rhythmical contractions disappeared, and large peristaltic waves occurred every 1 to 3 minutes. Be-

tween contractions the tone of the ileum was much below that in the control period but at the height of the contractions it far exceeded normal.

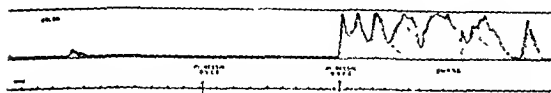


Fig. 5. The effect of pitressin on the colon of a normal subject.

Effect on the Colon

The effect on the colon consisted uniformly of an increase in muscular activity, amounting at times to intense spasm. Seven observations were made in 5 subjects. A representative tracing (Fig. 5) shows the abrupt onset of a series of contractions interrupted by brief periods of incomplete relaxation. Fluoroscopic observations made simultaneously were as follows:

pact, assumed a zeppelin-like shape and began a slow steady advance through the transverse colon and around the splenic flexure. After a momentary arrest coinciding with a period of relaxation indicated in the tracing, the barium column and tube progressed through the sigmoid colon to the rectum.

Fig. 6 shows in another subject the appearance of a segment of the descending colon before the administration of pitressin and during a contraction which followed its injection. The decrease in calibre and the loss of haustral markings of the colon and the increased compactness of the barium column are evidence of the intense contraction which was simultaneously recorded.

COMMENT

The action on the gastro-intestinal tract of posterior pituitary derivatives varies with the species tested and the conditions of the experiment. The literature on the subject up to 1929 is well reviewed

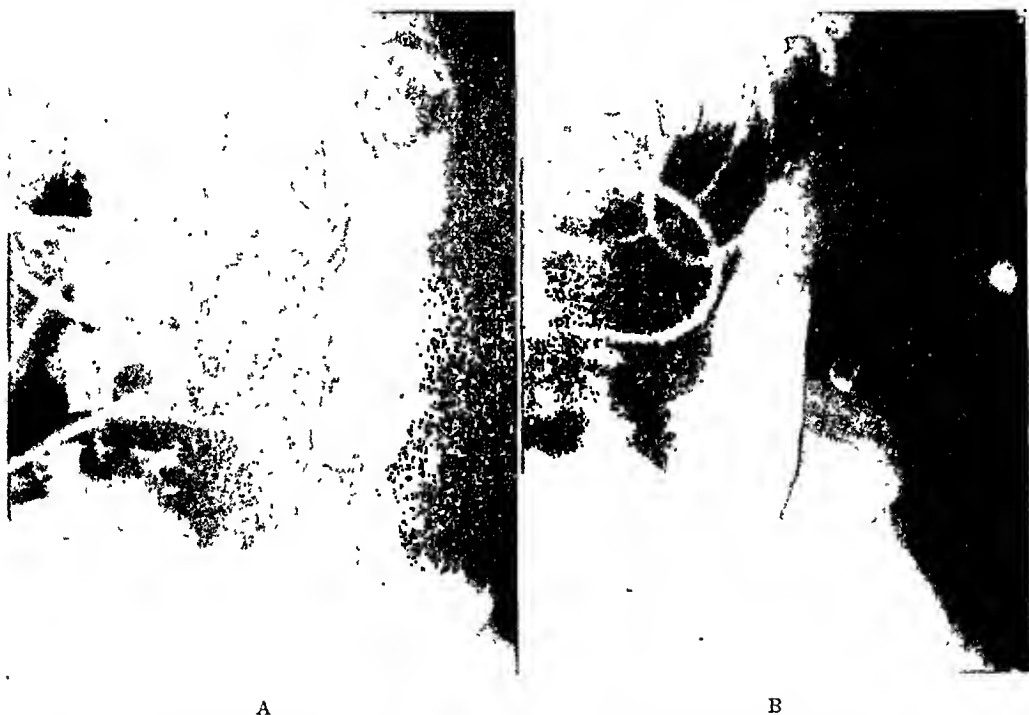


Fig. 6. Roentgenograms of a portion of the descending colon of a normal subject. (A) before pitressin, (B) after pitressin. Note that the tip of the tube and the balloon in (A) are at the splenic flexure. In (B) the tip of the tube has advanced and air has been forced from the balloon. Haustral markings are obliterated and the barium column is compact.

Barium outlined the entire ascending colon which prior to the administration of pitressin was of normal calibre and presented prominent haustral markings. During the control period no change was observed in the size of the balloon, which was situated in the ascending colon, or in the contour of the barium column. One-half cc. of pitressin was given without discernible effect in 10 minutes. After administration of an additional 0.5 cc. the outline of the ascending colon suddenly became smooth, the calibre decreased, the haustral markings were lost and air was forced from the balloon. At this point the first contraction was recorded on the tracing and the subject complained of "gas pains." The barium column became more com-

by Gruber and Robinson (4) and the rather confused status of the question is evident. Observations on the human published in the last decade, however, are in general agreement that augmentation of intestinal and colonic motor activity is produced by posterior pituitary preparations (5, 8). Their use in post-operative distention, and in eliminating gas from the bowel to permit proper roentgen visualization depends upon increased muscular contraction. Our observations have demonstrated a consistent increase in motor activity in the entire intestinal tract, with the two following qualifications: In the duodenum the prolonged after-relaxation which followed the initial contraction constituted the most characteristic effect of

pitressin. In the ileum the tone was sometimes decreased although peristaltic activity was augmented. However, the end result of the observed changes was invariably an increase in the forward propulsion of the intestinal contents.

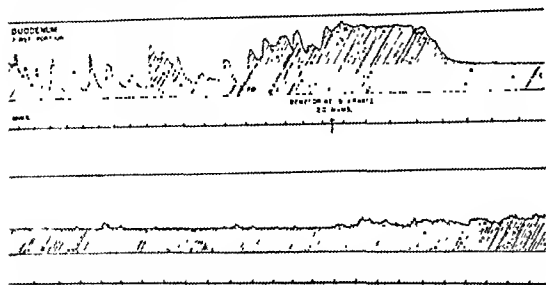


Fig. 7. The effect of amphetamine (benzedrine) sulphate on the duodenum of a normal subject.

II. AMPHETAMINE (BENZEDRINE) SULPHATE

Amphetamine (benzedrine) sulphate*, 0.015 to 0.020, was given to 18 subjects, a total of 21 observations being made on different portions of the normal intestinal tract. (Figs. 7, 8 and 9). Simultaneous tracings from the colon and ileum were obtained from the subject with an ileostomy. (Fig. 10). The results may be summarized as follows: In 12 experiments (57 per cent) no detectable changes were observed. In 9 observations (43 per cent) a reduction in tone and motor activity occurred. These changes were observed quite consistently in the ileum, but only irregularly in the duodenum, jejunum and colon. The effects qualitatively resembled those produced by atropine (2) but were as a rule of shorter duration and less regular in occurrence. This irregularity was not altogether due to individual susceptibility to the drug, since in one subject a striking effect was ob-

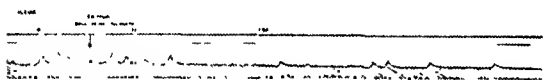


Fig. 8. The effect of amphetamine (benzedrine) sulphate on the ileum of a normal subject.

tained on 2 occasions and none on a third. In no case was the subject aware of the nature of the drug administered. In 2 instances unpleasant side effects consisted of nervousness and emotional instability. In several cases pleasant sensations of relaxation, increased mental acuity and mild euphoria were described.

COMMENT

Our observations are in general agreement with published data on the effects of amphetamine sulphate on the intact gastro-intestinal tract. Delay in final gastric emptying (9, 10), relaxation of the duodenal cap, small intestine and colon and decrease in small intestinal motility have been described (11, 12). Excised gut is stimulated by sufficiently high concentrations of the drug (13, 14). The use of amphetamine sulphate facilitates roentgen examination when abnormally high tone is a deterrent to proper visuali-

zation. However, the clinical usefulness of the drug in various disease states of the gastro-intestinal tract is not a matter of general agreement (15). The inconstancy of its action which we have encountered constitutes a limitation, but when its effects are produced they are of potentially beneficial nature.

SUMMARY

The method of intestinal intubation has been employed in a study of the action of pitressin and of amphetamine (benzedrine) sulphate on the human small intestine and colon. Pitressin produced an increase in motor activity of the intestinal tract. Usually both tone and peristaltic activity were augmented; in some instances, however, the peristaltic increase was associated with a decrease in intestinal tone. After brief contraction of the duodenum prolonged after-relaxation was observed. In general the effects

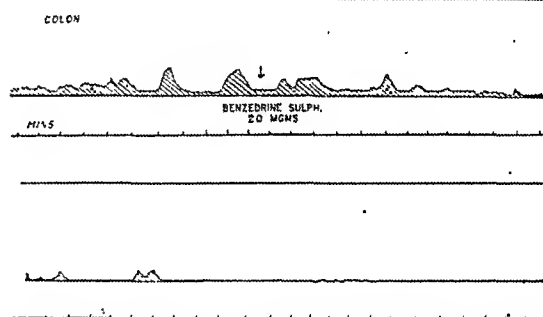


Fig. 9. The effect of amphetamine (benzedrine) sulphate on the colon of a normal subject.

of pitressin were more intense in the more distal portions of the tract. The activity in the ileum and colon bore a roughly reciprocal relationship in some instances.

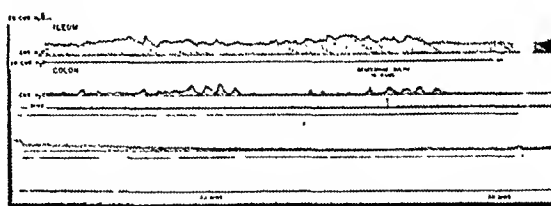


Fig. 10. Simultaneous tracings from the ileum and colon of a subject with an ileostomy for ulcerative colitis. The effect of amphetamine (benzedrine) sulphate.

Amphetamine (benzedrine) sulphate exerted a sympathomimetic effect on the small bowel and colon. Tone and peristaltic activity were decreased. The action of the drug was qualitatively consistent, though quantitatively it was less so, definite effects being produced in approximately one-half of the observations.

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*Supplied through the courtesy of Smith, Kline & French Laboratories, Philadelphia.

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DISCUSSION

DR. HEINRICH NEECHELES (Chicago): We have studied two of the drugs used by Dr. Elsom but have obtained different results and I would like to ask him for a

possible explanation. The first drug was benzedrine which we tried on man and dogs. Contrary to the findings of Myerson we showed that it produced pylorospasm and apparently also spasm of the small intestine. Its effect on the colon was variable, relaxation and slight contraction occurring at different parts of the colon as well as in different tests. Our technique was different from that of Dr. Elsom, in that we used X-rays and barium.

We also studied the effect of atropine and of a new synthetic drug, known under the trade name of Trasentin (Diphenylacetyldiethylaminoethanol-Hydrochloride) in a number of patients with intestinal fistulas, gauging the effects of the drugs by the amount of fluid or the consistency of the feces voided through these fistulas. In the greater number of these patients atropine had none or very little effect, while the second drug terminated the discharge of watery fluid and produced, within a very short time, formed stools.

DR. KENDALL A. ELSOM (Philadelphia): It is very difficult, of course, to reconcile differences in the results when different methods have been used. I think that is one of the reasons for the great confusion that exists in the literature today.

I can't explain the differences between ourselves and Dr. Neecheles. The doses of benzedrine we have used have been quite large, 15 and 20 milligrams given hypodermically. That may or may not explain the differences.

Observations on the Oral Administration of Citrated Blood in Man

I. The Effects on the Blood Urea Nitrogen

By

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and

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IN the past few years numerous reports (1-11) have appeared indicating the frequency of blood urea nitrogen elevation following hematemesis or melena. Several factors have been invoked to explain this phenomenon. These comprise dehydration, starvation, shock, impairment of renal function, and absorption of products of decomposition of the blood liberated in the intestinal tract. We have confirmed the frequency of this change and have adduced evidence to show that it does not necessarily depend on starvation, dehydration, shock, or impairment of kidney function (12, 13).

Attempts to evaluate the importance of the relationship of the blood in the intestinal tract to the elevated blood urea nitrogen content following hematemesis have been made by several investigators. Sanguinetti (2) reported a maximum increase in the blood urea of 20 to 25 mg. % within two or three days in two persons given 1000 and 2000 cc. respectively of citrated pig's blood by stomach tube. Clausen (9) noted an increase in the blood urea of about 25 mg. % within eight hours after "infusing" 500 to 600 cc. of ox blood into the stomachs of two patients who had had a recent

hemorrhage. On the contrary, Sucic (4) obtained no increase in two patients in one and two days respectively, after administering 500 and 1000 cc. of calf's blood.

We have given citrated human blood to a group of fifteen individuals free of obvious renal disease (Table I). The blood used was that which had been stored in the blood bank of the Cincinnati General Hospital and had been discarded after a period of three weeks as too old to be used for transfusion purposes. It was previously tested for its urea content. It was kept at room temperature for an hour before it was allowed to flow by gravity into the fasting stomach through a Rehfuess tube, and into the jejunum or upper ileum and colon through a Miller-Abbott tube. About thirty minutes were required for the introduction. One thousand cubic centimeters were administered as a single dose to seven members of the group, while a total dosage of 2000 cc. was given to eight. A hypodermic injection consisting of codeine sulfate gr. 1 and atropine sulfate gr. 1/150 preceded the administration of the blood in order to prevent too rapid transit through the intestinal tract and thus permit of more adequate digestion and absorption.

No ill effects followed the administration of the blood. There was no nausea or vomiting. One individual had five loose movements containing bright

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From the Department of Internal Medicine, University of Cincinnati Medical School and the Gastric Laboratory, Cincinnati General Hospital.

*Justin A. Rollman Fellows in Medicine, 1938-1939, 1937-1938, respectively.

AMERICAN JOURNAL OF DIGESTIVE DISEASES

TABLE I
Clinical data on fifteen patients studied

Case No.	Hospital No.	Age	Sex	Diagnosis	B.P.	Fundi	Urinalysis	Fasting B.U.N.
1	99066	29	M	Hematemesis—cause undetermined	106/60	Normal	Negative	9
2	101015	62	M	Hematemesis—cause undetermined	128/50	Normal	Negative	13
3	103691	19	M	Optic atrophy	120/70	Optic atrophy	Negative	12
4	98885	50	M	Duodenal ulcer (previous hematemesis)	150/60	Slight retinal angiosclerosis	Negative	13
5	101434	55	M	Duodenal ulcer (previous hematemesis)	130/78	Slight retinal angiosclerosis	Negative	10
6	Q1637	56	M	Superficial gastritis	132/90	Normal	Negative	10
7	98009	55	M	Atrophic gastritis	145/95	Normal	Negative	10
8	82152	34	M	Gastric ulcer	138/98	Normal	Negative	16
9	103825	49	M	Convalescent pellagra	150/96	Normal	Negative	24
10	54283	54	M	Atrophic gastritis	160/98	Normal	Negative	16
11	111986	49	M	Convalescent rheumatic fever	106/60	Slight retinal angiosclerosis	Negative	15
12	98689	41	M	Lung abscess	115/72	Normal	Negative	12
13	100726	27	M	Tuberculous cervical adenitis	112/74	Normal	Negative	14
14	115402	46	M	Convalescent lobar pneumonia	110/60	Normal	Negative	22
15	111542	23	F	Gonorrheal arthritis	98/60	Normal	Negative	10

blood twelve hours after receiving the blood into the jejunum. (This shows that, in the presence of intestinal hypermotility, bright blood may appear in the stools, though coming from high in the intestinal tract.)

After receiving the blood all of the patients were allowed to take food as desired, but, as a rule, did not eat until several hours afterwards. Determinations of the blood urea nitrogen were carried out before and at frequent intervals after the introduction of the blood. The determinations were made in duplicate by the aeration method of Van Slyke and Cullen (14). Specimens were obtained irrespective of meals because of the observation of MacKay and MacKay (15) that single meals containing a usual amount of protein have only a minor effect on the blood urea nitrogen. In a control group of nine subjects determinations made within two to three hours after meals were found to range between 9.6 and 21 mg. %.

Eight individuals received a total of 2000 cc. of citrated blood given at four-hour intervals in doses of 700, 700 and 600 cc. respectively (Fig. 1). In all eight a rise in the blood urea nitrogen occurred which exceeded the upper limits of normal (23 mg. %) (16). A maximum concentration of 24 to 57 mg. % was obtained within twenty-four hours of the first dose of blood. This was followed by a drop to normal on the second day in five and on the third day in the remaining three. These curves are similar to those obtained in patients with a single non-fatal hemorrhage from the stomach or duodenum and therefore emphasize the influence of the blood in the intestinal tract on the height of the blood urea nitrogen.

It is, of course, not known just how long there is actual bleeding in severe cases of hematemesis or melena. One wonders whether the patient usually has a single brisk hemorrhage lasting a short time or whether repeated bouts of bleeding occur at relatively short intervals. The resemblance of the curves shown in Fig. 1 to those seen clinically in cases of hematemesis or melena suggests that the actual bleeding is repeated.

It has been suggested that toxic products arising from the decomposition of the blood in the intestines may lead to impairment of kidney function (11), and thus account for elevation of the blood urea nitrogen. To exclude such a factor, determinations of renal function were carried out by the methods of Smith and associates (17) two days before and eighteen hours after the intragastric administration of 2000 cc. of blood. The eighteen-hour interval was selected because it represented a time period when the blood urea concentration was approaching its maximum (see Fig. 1). The results indicate that no significant change in renal function took place (Table II).

The effect on the blood urea nitrogen of varying the site at which blood was introduced was studied in seven individuals (Fig. 2). They were divided

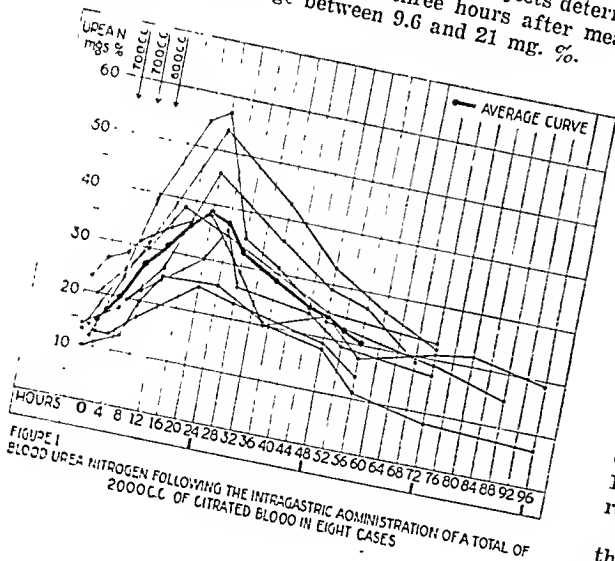


FIGURE 1
BLOOD UREA NITROGEN FOLLOWING THE INTRAGASTRIC ADMINISTRATION OF A TOTAL OF 2000 C.C. OF CITRATED BLOOD IN EIGHT CASES

TABLE II

Renal function before and eighteen hours after beginning intragastric administration of 2000 cc. of blood

Case No.	Before Blood Administration				After Blood Administration			
	B.U.N. mg. %	Clearances cc. Per Minute			B.U.N. mg. %	Clearances cc. Per Minute		
		Urea	Inulin	Phenol Red		Urea	Inulin	Phenol Red
1	12	88	104	357	26	94	114	333
2	13	38	68	221	51	38	70	262
3	11	81	103	292	35	81	127	351
4	14	72	93	270	54	70	110	298
5	13	47	74	242	37	38	71	279

groups of three, case No. 12 serving in each group. Each group received 1000 cc. of citrated blood as a single dose into (1) the stomach, (2) the jejunum or upper ileum, or (3) the colon. When the blood was given into the stomach, the urea nitrogen began to rise within two to four hours and reached a maximum

relationship of the digestion of the blood in the intestinal tract to the elevated blood urea nitrogen content.

The fact that no significant increase in the blood urea nitrogen followed introduction of blood into the colon coincides with our clinical experience in cases of hemorrhage from the colon and has proved of value in differentiating colonic from gastric or duodenal hemorrhage.

The effect on the blood urea nitrogen of varying the amount of blood introduced into the stomach was observed in one subject (Fig. 3). Following a control period of four days, during which he was on the regular ward diet, he was given 250 cc. of blood daily for eight days. With two exceptions a definite rise in the blood urea nitrogen was observed within twelve hours of the administration of each dose of blood and disappeared within twenty-four hours. Failure to obtain a rise after the first dose of blood may be explained by our waiting twenty-four instead of twelve hours before obtaining a blood sample. (This may also explain Sucic's failure to obtain a rise). This emphasizes the practical importance of carrying out urea determinations at intervals* not exceeding twelve hours when one suspects concealed hemorrhage from the stomach or duodenum. Failure to obtain an increase after the fifth dose of blood may have been due to a technical error.

*Determinations are best carried out at four-hour intervals, as we have seen the blood urea nitrogen double itself in this period following the administration of 1000 cc. of blood into the stomach.

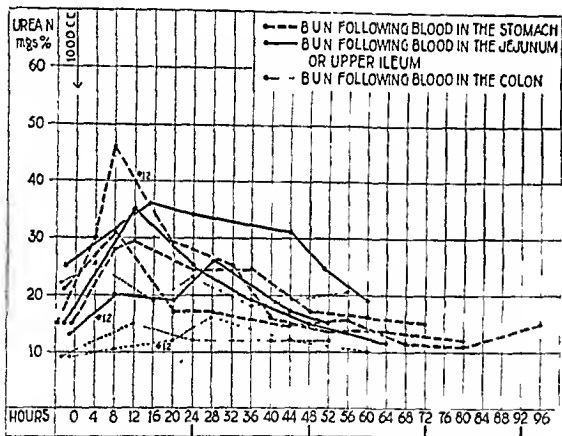


FIGURE 2
BLOOD UREA NITROGEN FOLLOWING ADMINISTRATION TO SEVEN PATIENTS OF 1000 CC. OF CITRATED BLOOD INTO (1) THE STOMACH, (2) JEJUNUM OR UPPER ILEUM AND (3) COLON

of 30 to 46 mg. % within twelve hours. This was followed by a return to normal within eighteen to thirty-eight hours.

When the blood was given into the jejunum or upper ileum, a maximum rise ranging from 26 to 36 mg. % was obtained within twelve to twenty-eight hours with a return to normal in twenty-eight to fifty-two hours. Following introduction of the blood into the colon no significant change in the blood urea nitrogen was observed during a period of fifty-two to sixty hours; the slight fluctuations which did occur may be considered to be within the normal range.

The fact that the maximum increase in the blood urea nitrogen was greater and occurred earlier when the blood was introduced into the stomach than when it was given into the jejunum or upper ileum may be explained by greater opportunity for digestion and absorption. Failure to obtain a rise when the blood was introduced into the colon may be explained by the virtual absence of digestion and absorption in this region. These observations again emphasize the re-

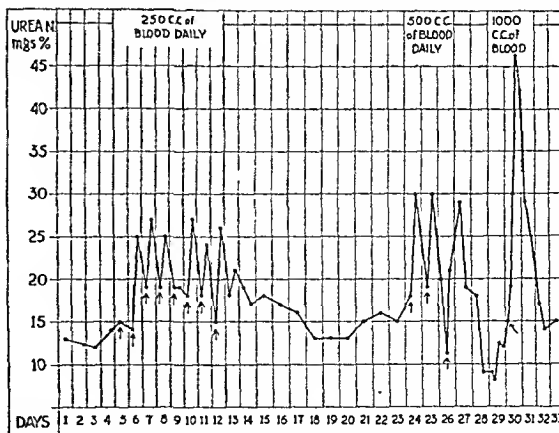


FIGURE 3
BLOOD UREA NITROGEN FOLLOWING INTRAGASTRIC ADMINISTRATION OF VARYING QUANTITIES OF CITRATED BLOOD IN ONE PATIENT

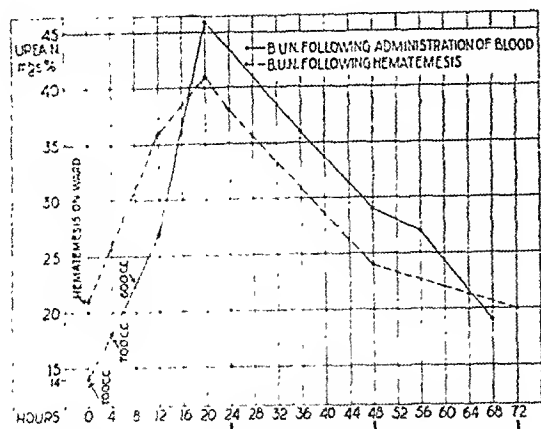


FIGURE 4
BLOOD UREA NITROGEN FOLLOWING HEMATEMESIS AS COMPARED WITH THAT FOLLOWING
INTRAGASTRIC ADMINISTRATION OF 2000 CC. OF CITRATED BLOOD IN THE SAME PATIENT

After a second control period of eleven days, 500 cc. of blood were administered on each of three successive days. Greater increases (of 11 to 18 mg. %) were obtained than those which followed the 250 cc. doses (6 to 11 mg. %). Four days after the last 500 cc. dose was given, a dose of 1000 cc. of blood was administered. An increase was noted within two hours and in twelve hours significantly exceeded that which followed the 500 cc. doses.

These observations show that the degree of blood urea nitrogen increase depends on the amount of blood administered at a given time. The time element may explain the disparity between the degree of anemia and the level of the blood urea nitrogen which is seen clinically in some cases of hematemesis. Thus, if a patient loses 2000 cc. of blood over a period of eight days, one might not expect the same degree of elevation of the blood urea nitrogen which would follow the sudden loss of this quantity of blood although comparable degrees of anemia develop.

Of much interest is a comparison in the same patients of curves of the blood urea nitrogen following massive hematemesis with those following the intragastric administration of 2000 cc. of blood (Figs. 4, 5 and 6). It is seen at once that the curves are strikingly similar, another substantiation of the importance of the alimentary factor in the elevation of the blood urea nitrogen following hematemesis. The quantity of 2000 cc. was arbitrarily chosen as, of course, we did not know just how much blood the patients had lost at the time of hematemesis. The quantity lost was evidently large as the number of red blood cells fell to between 1.0 and 1.7 millions per cubic millimeter.

In order to determine whether the elevation of the blood urea nitrogen following the administration of the blood was probably dependent on the protein content of the blood administered, determinations of blood urea nitrogen were made following the ingestion of large amounts of meat. It was planned to give a quantity of meat equivalent in protein content to the blood given, but this could not always be accomplished because of inability on the part of the subject to eat

the entire amount. The meat* was cooked for about two and a half to three hours and given in three doses at four-hour intervals. In Case 4 a total of 1.8 kg. of meat (equivalent to approximately 1700 cc. of blood) (19) was ingested. The blood urea nitrogen curve paralleled in a most striking way the curves obtained after administration of 2000 cc. of blood and after hematemesis (Fig. 7). In two other subjects given respectively 1.92 and 1.23 kg. of meat, appreciable rises in the blood urea nitrogen also occurred (Fig. 8).

These observations suggest that the elevation of the blood urea nitrogen following oral administration of blood may be attributed to the protein content of blood.

SUMMARY

The intragastric or intrajejunal administration in man of citrated human blood in single doses of 250 to 1000 cc. is followed by a significant rise in the blood urea nitrogen, which may begin within two to four hours, reaches a maximum within ten to twenty-eight hours, and usually returns to normal within forty-eight hours.

This increase in the blood urea nitrogen is proportional to the amount of blood administered. It also depends on the portion of the intestinal tract into

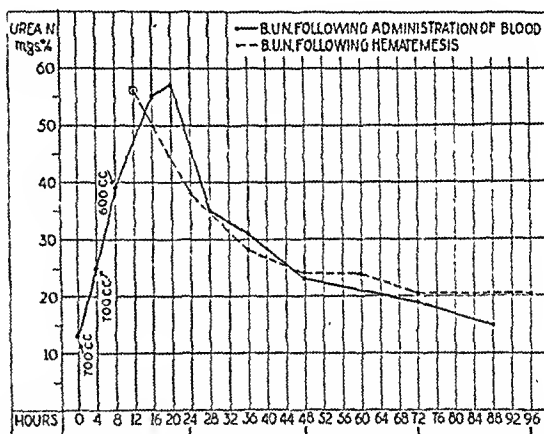


FIGURE 5

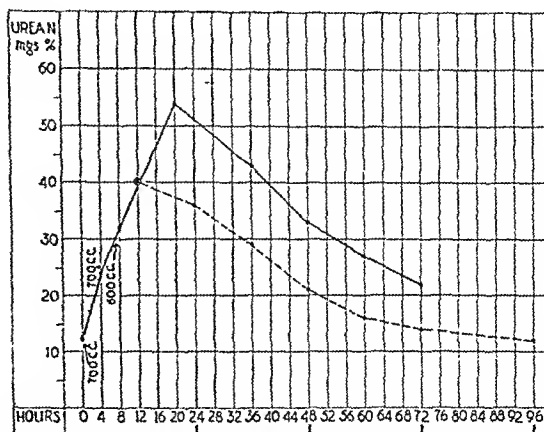


FIGURE 6

BLOOD UREA NITROGEN FOLLOWING HEMATEMESIS AS COMPARED WITH THAT FOLLOWING
INTRAGASTRIC ADMINISTRATION OF 2000 CC. OF CITRATED BLOOD IN THE SAME PATIENT

*Hind-quarter lean roundsteak = 20% protein (edible portion) (18).

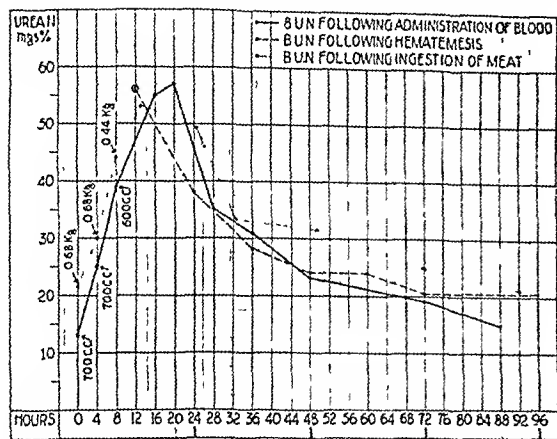


FIGURE 7
COMPARISON OF BLOOD UREA NITROGEN FOLLOWING (a) HEMATEMESIS (b) INTRAGASTRIC ADMINISTRATION OF 2000 CC. OF BLOOD AND (c) INGESTION OF 1.8 KILOGRAMS OF MEAT IN THE SAME PATIENT (CASE 4)

which the blood is placed, occurring earlier and to a greater degree when the blood is introduced into the stomach than when it is introduced into the jejunum or upper ileum, and failing to occur when the blood is administered into the colon.

Curves of the blood urea nitrogen obtained in eight individuals after the intragastric administration of 2000 cc. of citrated human blood during an eight-hour period were quite similar to those previously obtained in twelve patients following a single severe, non-fatal hemorrhage from the stomach and duodenum.

In three patients there was a striking similarity between the blood urea nitrogen curves after hematemesis and those after the intragastric administration of 2000 cc. of blood, and in one instance after the ingestion of 1.8 kg. of lean meat.

The increase of blood urea nitrogen following intragastric administration of citrated human blood in man is not accompanied by impairment of kidney function.

CONCLUSION

The elevation of blood urea nitrogen which occurs after the introduction of blood into the stomach or upper intestinal tract is apparently dependent upon the digestion and absorption of the blood.

We wish to express our thanks to Dr. Paul Hoxworth, Director of the Red Cross Transfusion Service; to Doctors Benjamin Felson, Crawford Elsey and Jack Singer of the Department of Roentgenology, and to Misses Marjorie Hall and Dorothy McCrory of the Department of Dietetics for their cooperation in this study.

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DISCUSSION

DR. GEORGE B. EUSTERMANN (Rochester, Minn.): One of the pressing problems confronting us and requiring solution sooner or later is the nature of the immediate prognosis following a massive hemorrhage. Is the hemorrhage for which the patient has been hurried into the hospital going to prove fatal or not? So far, we have no reliable criteria.

Doctor Schiff and his associates have confirmed what other investigators have previously demonstrated, namely, the importance of the factor of intestinal absorption of blood in relation to the elevation of the blood urea nitrogen, the prognostic significance of the latter within certain limits, and the passive role, if any, of the kidneys. Our own experiences are largely in accord with his. While there are exceptions to all rules, there is general agreement with the observation that the older the patient the greater the risk from hemorrhage, for various reasons. While Bennett's recent conclusions on the prognostic significance of blood volume studies following hemorrhage await confirmation, the results of such studies appear to be promising. Recent articles by Crohn and Snell on the subject of gastro-enteric hemorrhage are thought provoking and worthy of our close perusal.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): About four years ago one of my internes, Dr. Alfred Ingegnio, made a study of the blood chemistry findings in a series of gastric hemorrhage cases at the Long Island College Hospital and reported his observations. He noted that in a large proportion of cases an azotemia occurred during

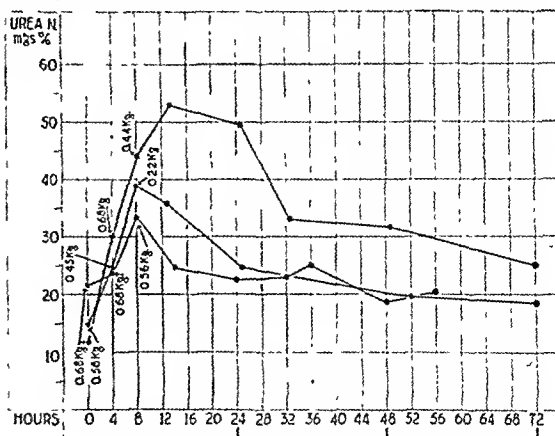


FIGURE 8
BLOOD UREA NITROGEN FOLLOWING INGESTION OF LEAN MEAT (125 TO 192 KILOGRAMS)

the early stages following the hemorrhage and that the urea rapidly returned to normal when other findings indicated that bleeding had ceased. In the patients showing continued or recurrent bleeding the urea remained high, and Ingegno suggested that the presence of a continued azotemia might be used as an indication of continued bleeding. I am glad that the very important and ingenious study by Dr. Schiff and his associates tends to confirm these observations.

DR. A. C. IVY (Chicago): Mr. President, I should like to ask Dr. Schiff what diet these patients were on—for two reasons: In the first place, we have done some experiments in an attempt to answer the question: How much blood does a human being have to lose before a tarry stool becomes manifest? Our average figure is 60 cc. but I deliberately told the students performing this experiment to take a milk and cream diet. The figure given by the essayist was 120 cc. That is twice ours.

Of course, there may be a difference in the criteria regarding what color constitutes a "tarry" stool. The second point that I have in mind is that I observed, that the author's urea nitrogens were all in the lower range of normal, indicating to me that his patients were probably receiving a relatively low protein diet. On a high protein diet the urea values tend to be higher around thirty or forty.

However, I think the crucial point in the authors' experiment is that an equivalent amount of protein in the form of meat gave an equivalent rise in the blood urea nitrogen.

Another point—many of you have probably thought of this—if the patient has a chronic nephritis or if some of the factor of safety in the patient's kidney has been destroyed, then a loss of 500 cc. of blood would be more serious than in a patient who had a normal kidney and a normal factor of safety, because the loss of 500 cc. of blood would create an anoxemia which might lead to renal failure in the former patient, and probably not affect the latter patient, with the good kidney.

DR. BURRILL B. CROHN (New York): I am more or less called upon to discuss the paper, having just published on gastric hemorrhage and announced myself as not particularly convinced of the prognostic significance of urea estimations of the blood.

I have observed cases of hemorrhage from ulcer over several weeks of time, in one instance with hemoglobins of 15 to 18 per cent, without an elevation of urea in the blood, yet with continuous bleeding into the intestinal tract.

In other cases of severe bleeding prolonged over a length of time, the urea figures did not rise, in spite of very low hemoglobin readings.

From a study of a series of cases of hemorrhage, I definitely have the opinion that the rise of urea is proportionate to the degree of shock, and that really significant rises of urea such as Meulengracht speaks of in his article, only occur directly after and as a result of shock, the mechanism being a prerenal azotemia.

It is true that I paid little attention to rises of urea up to 40 or 50 milligrams per hundred cc., which are the figures Dr. Schiff shows us today. Such figures up to 40 considering the amount of concentrated proteins suddenly being shunted into the intestine. Two thousand cc. of blood weighs four and one-half pounds. That is quite a high protein diet (?) for a person in shock or hemorrhage to absorb without an elevation of urea.

Perhaps I may suggest to Dr. Schiff that there are two elements in the rise of urea following hemorrhage. One is the factor of rapid absorption of a huge amount of concentrated protein suddenly thrown into the alimentary

tract, and the other, which is the real factor, the prerenal azotemia as a result of shock, and the fall of the blood pressure. The element of shock is the real factor, and the significant rises of urea occur only when the hemorrhage is acute, precipitate, and large in amount, and the rises of urea are proportionate to the degree of shock rather than degree of loss of blood.

As for saying that the renal tests show no difference in kidney function, I don't think that the modern kidney tests are sufficiently delicate to really indicate an imbalance in the kidney function.

In pyloric stenosis you know and we know that definite kidney changes take place, calcification and degeneration, and there is a definite clinical picture associated with pyloric stenosis and yet no tests show any imbalance or changes of kidney function even though there are definite organic changes in the kidney.

DR. LEON SCHIFF (Cincinnati, O.): We are very grateful to the members who have been kind enough to discuss this work. We have been impressed with the prognostic value of the blood urea nitrogen in our clinical studies. In fifty-three cases which we are reporting elsewhere,* five had a blood urea nitrogen content of over 100 milligrams per cent, and four of these died. The fifth had chronic nephritis with renal insufficiency which probably influenced the degree of his elevation. It is interesting that we found no constant relationship between the age of the patients and the degree of elevation of the blood urea nitrogen. We should like to give due credit to Dr. Ingegno, who, in a brief paper in 1935 stressed the occurrence of this phenomenon and its prognostic significance.

In reviewing the literature on blood urea studies it is frequently difficult to determine whether the author is dealing with blood urea or with blood urea nitrogen. The former is normally 2.14 times the latter. Our figures deal only with the blood urea nitrogen which, in our hands, has been found to normally vary between 9 and 21 milligrams per cent. We believe, therefore, that a concentration of 30 milligrams per cent or over represents a significant increase.

These patients, Dr. Ivy, were on a regular ward diet, with the usual amount of protein. We have occasionally obtained tarry stools following the oral administration of 75 cc. of blood, but, in order to uniformly obtain tarry stools, we have had to give 100 to 150 cc. of blood.

As Dr. Crohn mentioned, one occasionally finds a low blood urea nitrogen in the presence of a very low hemoglobin concentration. We believe that the rate at which the hemorrhage occurs explains this disparity. Thus, for example, if the hemorrhage occurs quickly, one may expect a rise in the blood urea nitrogen, but if it occurs slowly, one may not expect this rise although an equivalent amount of blood may be lost.

It is true that shock will, through its secondary effect on renal function, elevate the blood urea nitrogen. We have shown, however, in the study to which I alluded, that shock is not an essential factor in the elevation of the blood urea nitrogen which follows hematemesis. It is true, nevertheless, that the highest blood urea nitrogen values are more commonly seen in individuals with shock than in individuals without this manifestation.

Dehydration and starvation may likewise play a role in the elevation of the blood urea nitrogen, but we have satisfied ourselves that their role is not essential as we have seen the blood urea nitrogen rise in five or six hospital patients who were on a Meulengracht diet with an abundance of fluids at the time of a second hemorrhage.

*Archives of Internal Medicine (in press).

The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester, and Phospho-lipid Tests in Diseases of the Liver*

1. The Results of the Tests

By

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FOR many years investigators have attempted to find a test which would give a good index of the condition of the liver in the human patient. It is now generally accepted that no *single* laboratory test has been devised which will serve this purpose.

In the last five years on the second and fourth (Harvard) Medical Services at the Boston City Hospital about 300 consecutive cases of jaundice have been intensively studied and various liver function tests used.

This communication deals with the results of a special study in the past year of 66 cases of hepatic disease, nearly all of which exhibited jaundice. The tests used were total cholesterol, ester cholesterol per cent, phospho-lipids, hippuric acid excretion, icteric index, urobilinogen and bromsulphalein excretion.

Our object was to obtain, if possible, a better idea of the condition of the liver and to compare the different tests, to see how far they could be used in diagnosis and prognosis.

We know that the liver functions are constantly changing during an attack of jaundice from the onset to the height of the jaundice and during convalescence, and, therefore, stress has been placed on the frequent repetition of the laboratory tests during the course of the illness and in some instances for many months after the attack had subsided. Although the series is not a large one we have gained in this way much additional information both from the standpoint of the individual patient and also as to prognostic significance of the various tests. Though the advantages of *serial liver function tests* are often mentioned in the literature, they seem to be more often mentioned than used. In our series where both hippuric acid and cholesterol ester tests were normal in mild and convalescent cases, the tests were not apt to be repeated.

The series is also interesting because it includes twenty patients with chronic cirrhosis. This condition must often be considered in the differential diagnosis of painless jaundice but it has received less attention from a laboratory standpoint than the cases of severe acute liver disease, in which the results are much more striking.

The following tests were chosen because they are suitable for use in a jaundiced patient, and because

there has been considerable discussion and disagreement about their value both in differential diagnosis and prognosis. Some tests such as the bilirubin excretion or bromsulphalein tests were considered unsuitable or unnecessary in the presence of jaundice. The modified bromsulphalein test was only used to determine residual liver damage after the jaundice was gone.

METHODS

The hippuric acid excretion was studied by the gravimetric method of Quick (1, 2) because the precipitate in addition to hippuric acid yields unknown, but very small amounts of unconjugated benzoic acid and glucuronic acid which might give erroneous acidity values by the titration method. The absence of characteristic hippuric acid crystals required fractional evaporation until these could be identified. This test is based on the theory that sodium benzoate is conjugated with the glycine of the body by the liver and is excreted as hippuric acid. An excretion of 2.5 to 3 grams was considered normal. This test was only considered significant where we had approximately normal renal function as measured by analysis of the urine, the non-protein nitrogen of the blood and a concentration test of the urine.

The Rosenthal (3) bromsulphalein test was modified to include the study of blood samples withdrawn at 2, 5 and 15 minute intervals after the injection of 2 mgm. of the dye per kilo of body weight.

This was found to be a more delicate test than the one-half hour residue in a group of non jaundiced patients after recovery from acute hepatitis.

The normal two-minute sample may show as much as 80% retention in the older age group, while younger persons may have as high as 30-40%. The five-minute sample rarely contained more than 15%, while the 15-minute sample normally might show as much as 5% retention.

The phospho-lipid determination includes the extraction of plasma lipid by the method of Bloor (4). A portion of the extract which was evaporated to dryness, was digested* with sulfuric acid and potassium persulfate, and the phosphate determined using aminonaphthol sulfonic acid. The normal range is 8-9 mgm. %.

Total lipids were determined in several cases but

*From the Second and Fourth (Harvard) Medical Services and the Surgical Research Laboratory of the Boston City Hospital. Read at the forty-second annual meeting of the American Gastro-Enterological Association, Atlantic City, May 1, 1939.

*Unpublished data of C. H. Fiske and Y. Subbarow of the Department of Biochemistry, Harvard University.

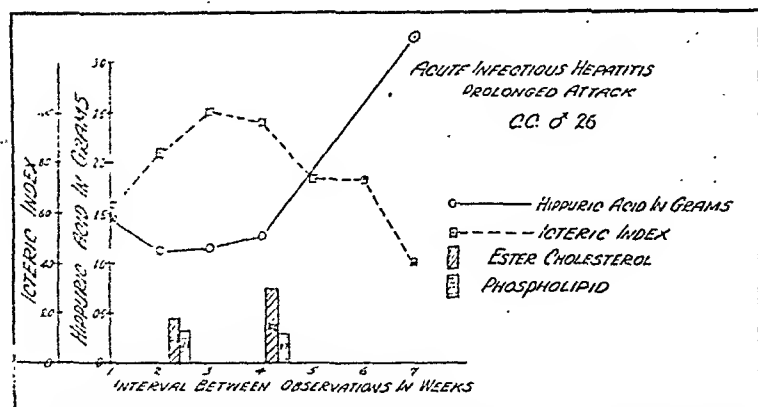


Chart 1. (Mr. C. C. Acute Infectious Hepatitis). The phospho-lipid was within normal limits; the ester per cent started low and rose to normal fairly early, at the end of four weeks while patient was still deeply jaundiced and the index 100; the hippuric acid excretion remained low for four to six weeks and became normal only at the end of seven weeks, while the patient was still moderately jaundiced.

were found to rise and fall with the phospho-lipid and total cholesterol, giving no added information, so were discontinued.

The total, free and ester cholesterol were determined by Smith and Marble's (5) modification of Bloor and Knudson's method (6) which saponifies the esters and, therefore, yields more uniform results. In the original Bloor and Knudson method where saponification is not used, the values may be 10% or more higher than with the Smith and Marble modification. We have considered an ester percentage of 60%-70% as normal. The blood must not be hemolyzed for the cholesterol tests, because the red cells contain only free cholesterol which, if liberated by hemolysis, gives an abnormally high value.

Urobilinogen was measured in the urine by the method of Wallace and Diamond (7). The bleeding time was measured by the Ivy method (8).

There are some practical limitations or disadvantages for each type of test; for example, in the tests which require blood chemistry such as the phospho-lipids, total cholesterol, and cholesterol esters, vein punctures must be repeated for serial tests and

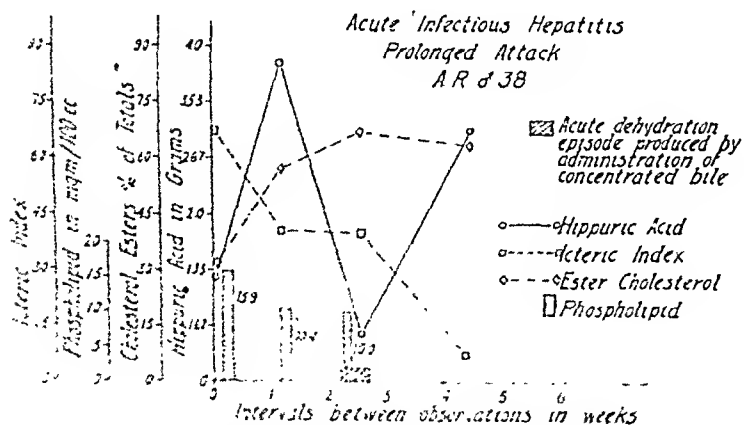


Chart 2. (Mr. A. R. Acute Infectious Hepatitis). The phospho-lipid was somewhat increased, but dropped at the end of a week to normal. The ester per cent started low and rose early to normal at the end of a week and a half and remained there. The hippuric acid excretion started low, became normal at the end of a week and a half; later during an attack of acute dehydration due to profuse acute vomiting and diarrhea, the hippuric acid excretion fell to a low point, and then recovered to normal. This episode illustrates the striking effect of dehydration and poor kidney function on the hippuric acid excretion test.

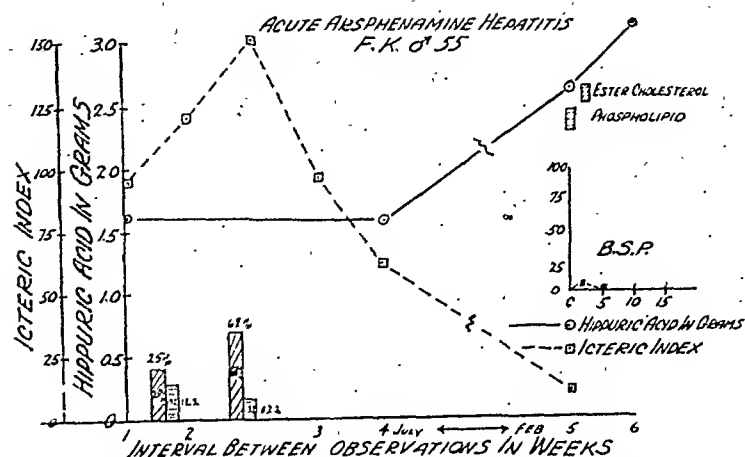


Chart 3. (Mr. F. K. Acute Toxic Hepatitis). The phospho-lipid was distinctly high at first (19.2) though not as high as most of our obstructive cases. The ester per cent started low and rose early to normal at the end of a week and a half while the biliary index was 100 to 125. The hippuric acid excretion remained low for over a month, but was found to be normal at the end of five and six months. A B.S.P.* test done seven or eight months after the attack of jaundice showed no retention.

it is desirable to keep the veins in good condition for treatment with glucose solution especially in the sicker patients who cannot take glucose by mouth. The urgent need of using the veins passes (for the time at least) when the jaundice is over, so the objection to a method requiring puncture of a vein, does not apply to the bromsulphalein method as we used it, to show residual damage. The cholesterol analysis is also somewhat elaborate and requires more time and experience than the other tests.

The dose of benzoic acid given for the hippuric acid excretion test may be mildly distasteful or very rarely cause vomiting, the latter only occurred once in these 66 cases. Quick has proposed a method of intravenous injection of hippuric acid to avoid this difficulty. Our impression is that it will be rarely needed except in very sick patients or at once after operation.

Normal renal function has seemed to us very important. The non-protein nitrogen has always been determined; also the ability to concentrate the urine. We felt that the hippuric test could not be relied on

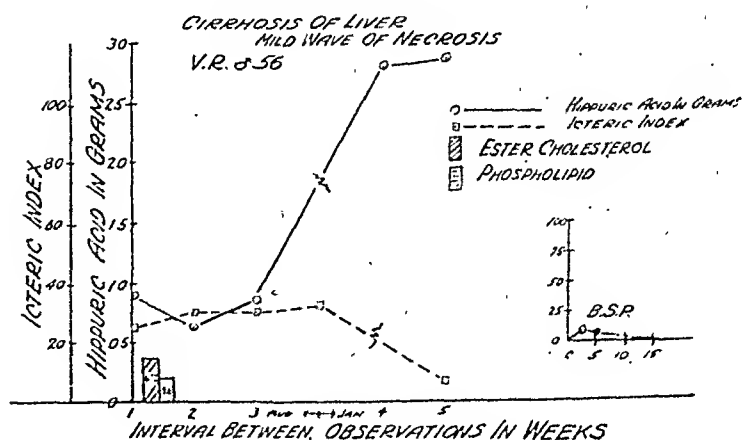


Chart 4. (Mr. V. R. Cirrhosis with a mild wave of Necrosis). The phospho-lipid was normal; the ester per cent was normal even at the start; the hippuric acid excretion was low for about a month and was normal at the end of four months later. The low hippuric acid excretion bore little relation to the jaundice which was mild. At the end of five months when the jaundice was gone, a B.S.P.* test was normal.

*B.S.P. = bromsulphalein.

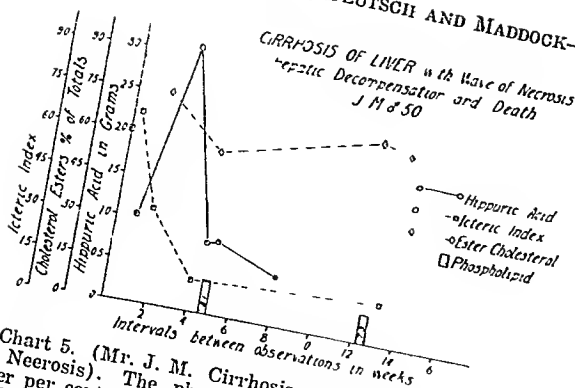


Chart 5. (Mr. J. M. Cirrhosis—a fatal case with wave of Necrosis). The phospho-lipid remained normal; the ester per cent remained normal throughout 14 weeks, up to the time of the patient's death, showing its lack of value in prognosis. The hippuric acid excretion was first low, then normal during a period of vigorous regeneration of the liver, then became low and remained so even though the jaundice was gone. (The hippuric acid excretion tests had to be discontinued after the eighth week as the patient became irrational and incontinent).

when nephritis or obvious dehydration was present or in so-called hepato-renal cases, a complex and rather poorly defined group of clinical disorders in which liver injury or infection, is associated with renal lesions or dysfunction.

A period of marked dehydration such as is seen in Case 13, Chart 2, will interfere with renal function and the use of this test. We have wished to test the renal circulation in some of our cases to see if it had an effect in lowering the hippuric acid excretion, but know of no simple way to do this and have noted that a moderate degree of circulatory failure such as was occasionally found, has not seemed to interfere with the excretion of hippuric acid.

The collection of the urine at the end of four hours

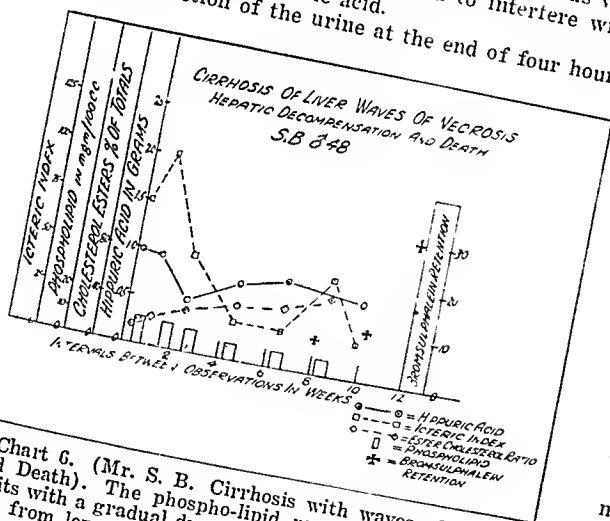


Chart 6. (Mr. S. B. Cirrhosis with waves of Necrosis and Death). The phospho-lipid remained within normal limits with a gradual drop. The ester per cent rose gradually from low to normal at the end of two months, just before his death, showing its entire lack of prognostic value in this case. The hippuric acid excretion was always low, one gram or less, and the hippuric acid excretion and compensation. B.S.P. tests in the last two weeks of life when the hippuric acid excretion was low showed progressive retention and a clear picture of the bad prognosis.

B.S.P. = bromsulphalein.

required simple cooperation on the part of the patient and nurse. In a sick patient who is incontinent, the test fails.

In Table I complete data are presented in each of the various types of liver disease. The tables indicate the dates of tests; the duration of the jaundice before entrance to the hospital, the icteric index, the hippuric acid excretion in the urine in grams, the phospholipids and total cholesterol in the blood in milligrams, and the percentage of cholesterol ester. The urobilinogen figures represent the dilution in which the test was positive; e.g., 64 means positive in a dilution of 1 to 64. The Ivy bleeding time was noted in seconds and the bromsulphalein test by the method described, II gives a summary of the significant changes in the entire series showing the per cent of cases in which the tests were low, normal, increased or went from low to normal. The figures under the titles of the different tests show what we have considered normal.

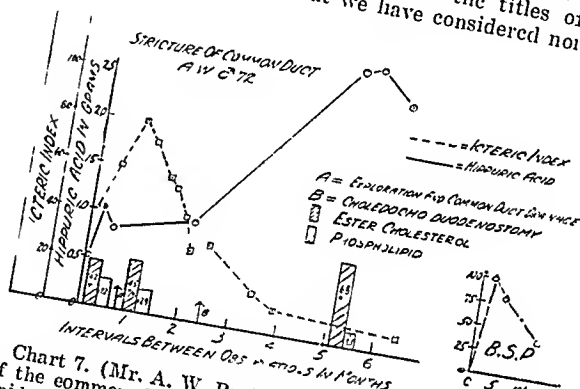


Chart 7. (Mr. A. W. Partial obstruction due to stricture of the common duct, with two operations). The phospholipid and total cholesterol were rather high at the outset due to partial obstruction and both became normal after the first operation, drainage of the common duct. The ester per cent was low at the outset, remained low after the first drainage operation and then finally became normal after the second (short circuit) operation. A biopsy of the liver showed biliary cirrhosis. The hippuric acid excretion followed a similar course, but at a lower level and reached normal in five months. Tests were omitted on account of severe illness during the third and fourth months. The B.S.P. test at the end of six months showed 40% retention. A later test, not shown on the chart, at the end of eight months showed no retention. The B.S.P. tests showed the very slow recovery from the liver damage and were positive at a period when all other tests were normal.

Results—In general the results of the various tests were as follows:

The lipid-phosphorus values were for the most part normal with the notable exception that in the cases of obstructive jaundice almost 90% were markedly increased, i.e. 13 to 33 mg. (Normal 8-9 mg.). In a few of the cases of acute infectious or toxic hepatitis there was also an increase, showing 14-16 mg. in the toxic cases (catarrhal jaundice) and 19-27 mg. in the case of acute yellow atrophy of the liver not included in the series showed a phospho-lipid value of 3.0 mg.

The total cholesterol behaved very similarly to the lipid-phosphorus and was increased in approximately the same cases of obstruction, showing variations be-

TABLE I

ACUTE TOXIC HEPATITIS												
No.	Date	Days of Jaundice	Index	Hippuric	Phos. Lipids	Cholesterol		Urob.	Bromsulph. Retention			Comment
						Total	Ester %		2'	5'	15'	
1	12-19-38 12-21 12-24 12-28 2-27-39	0	10 7 7 7	 2.79 1.44	7.0 8.2 9.6	148 138 157	65 62 61	8 128 64 32				Marked clinical improvement 3rd day porphyrinuria. Alb-Glob ratio 3.74-2.33.
2	1-5-39 1-11 1-30 2-18	7	80 80 40 10	0.4 0.90 1.97 3.66	7.7	229 390 420	34 42 59	4 8 32	(2-27-39) 80 20 0 (4-22-39) 3 0 0			Arsphenamine deep jaundice after third injection.
3	10-7-38 2-8-39 2-11	10	90-60	1.8 3.26 3.82	9.2	194	61	64-32 16				Arsphenamin 4 months later, jaundice for 2½ weeks.
4	5-6-39 5-11 5-25	1	15 10 5	0.70 2.20 3.72		188 229	64	8 16		30 10 2		C Cl ₄ inhaled. Renal damage low hippuric. NPN 70-43-30.
5	1-12-39 1-14 1-24	0	4	0.96 2.40 3.00		221 215	68 67					Toxic thyroid. BMR + 44 ÷ 4. Clinically severe. Rapid recovery with glucose.
6	7-1-38 7-14 2-3-39	37	100 60	1.93 2.26 2.46	10.7	214	52	0-16 4-32				Arsphenamin clinically mild (negro with glass eye).
7	7-18-38 7-27 2-9-39 2-13	21	90-130 75 7	1.67 1.64 2.69 3.30	19.2 13.2	282 302	25 67	0-2 8-64 8		0 0 0		Arsphenamin. Entered in coma. Rapid recovery with glucose.
8	9-19-38 9-27 10-4 10-11 5-15-39	21	150 160 180 70	0.0 0.78 1.74 2.30 2.40	11.0 13.3 11.6 9.6	137 216 299 280	21 34 67 67.5	0 4 64 32		5 10 0		Arsphenamin. Marked malaise on entry, then rapid convalescence.
9	8-14-38	7	55	Anuric	7.2	108	10	32				Acute alcoholism. ? Hepato-renal. Entered in coma, died in 4 days. NPN 175. Uric acid 15.4.
ACUTE INFECTIOUS HEPATITIS												
10	10-14-38 10-17 2-17-39	1	35 25 7	1.98 2.96	7.4	161	62	64				Mild brief jaundice. Convalescing from rheumatic heart disease.
11	8-22-38 8-29	5	60 30-15	1.86 3.09	10 14.4	119 234	20 41	4				Deep jaundice. Liver 4 cm. below costal margin. Recovery in 1 week. Takata neg.
12	7-20-38	0	6	0.54	8.8	137	34	16				Septicemia, died acute biliary cirrhosis, embolic glomerulo-nephritis. BUN 86.5 terminal.
13	11-17-38 11-25 11-30 12-6 12-19	21 ? 3 mos.	65 100 40 15 7	1.31 3.77 1.23 0.62 3.09	15.9 10.4 10.0	242 229 254	31 56 67	64 64 128 64 16				Progressive recovery except for acute dehydration after administration of concentrated bile.
14	5-10-39 5-12 5-15 5-22 6-6 6-12	30	180 140 80 15	1.71 1.61 1.28 2.31 2.82	10.1	154 144	9% 42%	4 16 128 16				Deep jaundice considered obstructive by surgeon. Ran typical course of severe infectious hepatitis.
15	6-6-39 6-12	2	75 20	2.73 2.57	17.0	237	26	256 4		15 5 2 8 5 2		Infectious hepatitis. Sulphani-lamid. ? Toxic hepatitis.
16	1-9-39 1-14 1-30 2-9 6-5	14	65 90 160 40 8	1.43 1.20 1.36 3.41 3.65	12.5 9.7	127 180	35 70	16 8 256-128 32 16				Very ill 2 weeks then slow convalescence. Late Graham test normal.
17	1-4-39 1-7 1-17 2-15	5	70 40 30 7	2.91 4.06	16.4	195	40	128 32 16 8		25 15 0 10 5 3		Liver 3 cm. below costal margin. Returned to normal in 1 week.
CHRONIC CIRRHOSES												
18	7-12-38	0	5	0.74	6.6	158	64	16				Portal, luetic aortitis and coronary. Died of cardiac decompensation. NPN 32. A-G ratio 2.21-4.25.
19	4-17-39 4-18 4-27 5-9 6-3		75 20	0.60 1.00 1.57 Incontinent 0.0	7.2 8.1	132 140	49 57	50		60 40 40		Hemachromatosis, ascites. Progressively worse. EKG shows myocardial failure.
20	10-19-38	0	5	1.99	10.5	331	72	32				Banti, large spleen 20 years. Recurrent attacks of anemia with G.I. bleeding. Total Prot. 6.
21	11-22-38 12-6 12-31 1-14-39	0	7	1.01 1.41 1.84 0.80	7.8	154	67	16 4		4		Hemachromatosis, hippuric acid excretion improved with improvement of glycemia and glycosuria. Later heart failure, died of cerebral accident.
22	5-5-39 5-12 8-23 1-26-39 2-7	4	25 30 35 7	0.93 0.76 0.90 2.82 2.86	9.6	233	67	64 64 32		5 3 0		Mild portal cirrhosis, with compensation in 5 months. Long history of mild drinking.
23	2-17-39 2-24 3-6 3-16	14	15 20 15	0.57 0.24 1.18 2.38	6.7	119	58	8 128-64 4				Portal, moderately severe with marked improvement.

TABLE I (CONTINUED)

CHRONIC CIRRHOSIS (Continued)

No	Date	Days of Jaundice	Index	Hippuric	Phos Lipids	Cholesterol		Urob	Bromsulph Retention 2' 5' 16'	Comment
						Total	Ester %			
24	3-25-39	3 wks.	50							Portal with acute necrosis Admitted to surgical service as obstructive Lues
	4-10		35	2.03		201	41	266		
	4-13		30			164	67	256		
	4-24		15	1.51				0		
25	4-13-39	0	8			276	76	4-18	90 30 6	Portal, 6 years ago jaundice explored, biopsy, recurrent ascites Takata +++ AG ratio 1.95-
26	4-4-39	90	200		11.0	129	26			
27	7-29-38	14	70	1.07	8.1	220	75	128		Portal, variable course Recurrent ascites
	8-11		15	3.06		181	67	64		
	8-30		15	0.78		224	63	32		
	10-25		10	0.82		191	69			
	11-2		15	0.68	7.3			64	1½ hour = 30	
28	9-26-38	21	90	0.31	6.7	176	54	64		Portal, jaundice subsided Ascites developed Cholema death
	10-13		85	1.37				64	1½ hour = 100	
	10-26		25			143	71	64		
29	10-4-38	0	13	0.80	6	114	66	266		Portal—Course of tests helped to rule out cancer
	10-15		10	1.85				32		
	10-31			1.71				32	1½ hour = 0	
30	9-27-38	7	50	1.74	9.0	189	60	32		Portal—Recurrent D.T.'s Liver damage variable Korsakoff's psychosis Marked anemia
	9-29		35	1.61				0		
	10-27		5	1.93				0		
	12-28		15	2.87				0		
	1-13-39		5	2.21				16		
	6-1			2.53	7.6	116	63		9 4 2	
31	10-26-38	7 6	60	0.95	11.7	193	14	8	(12-1-38)	Portal—Progressive downhill course Death P.M.
	11-2		100	0.91	11.3	163	22	32	(12-10-38)	
	11-12		50	0.51	9.0	167	36	16	(12-31-38)	
	11-25		20	0.76	6.7	141	42	128	10	
	12-12		50	0.87	6.7	140	62	32	30	
32	11-29-38	0	16-20	0.93		112	11	128		Portal—Long alcoholism Palpable liver Died broncho pneumonia
33	12-6-38	1 yr	75	1.04	9.2	118	50	256		Portal—Long alcoholism Deep jaundice purpura Transferred to another hospital
34	2-28-39	6 mos	60 30	1.92				0.8		Portal or subacute toxic recurrent jaundice Bleeding tendency Mild cirrhosis and diabetes with
	3-2		20 16	1.81				64.8		
35	5-9-39	0	20	1.00	15.5	218	62	164		
	5-16		7	1.65						
36	1-26-39	6	100+	0.79	9.4	125	43			stone, biopsy cirrhosis died 6 weeks later Cholema
	2-18		100+	0.96						
	2-28		100	0.25	9.5	142	42	1		
	3-15									
37	4-20-39	1	4	1.60		100	60	32		Fatty degeneration of liver Lues arphenamine Terminal miliary tuberculosis Death
	4-27			1.40		98	55			
38	4-17-39	1	55	7.39	9.7	144	46	128		Cirrhosis probable Cancer not entirely ruled out
	5-18		42					64		
	6-1			3.29	7.8	184	50	16		

TUMORS

39	6-1-38	0	25	0.66	6.6	144	61	64 72		Hemangio blastoma diagnosis of cirrhosis at operation 4 years previous Biopsy of neck gland hemangio bl stoma A-G ratio 1.82-3.97
	1-27-39		14	0.80				8		
	2-4		15	1.41				16		
	5-5			(too sick)	6.9	102	44			
40	10-13-38	0	5	1.47	9.6	234	65			Sarcoma of eye removed 3 years before Nodular liver No jaundice
41	2-17-39	0		2.91						Leukemoid blood picture marked anemia Large rubbery liver with good function Comfortable but weak
42	11-22-38	0	10.4	2.20	8.9	160	64			Sarcoid of lungs liver spleen and skin (biopsy) No jaundice Serological lues

HEMOLYTIC JAUNDICE

43	6-5-39	0	150		6.0	103	31			Hemolytic jaundice Sulphanilamide Toxic hepatitis
	6-7		95		5.7	146	55			
	6-9		25	0.0						
	6-10			1.33						
44	5-9-39	1 yr	70 35	2.60	6.9	110	70			Typical hemolytic jaundice with moderate icterus and normal liver function Reticulocytes 67% to 63% Total lipid 431
	6-10		50 20		5.6	135	66	16		
	5-27								30 5 2	
45	5-16-39	2	50	3.31	6.9	178	61			Acute hemolytic anemia, normal liver function Two transfusions Reticulocytes 24%-16% Total lipid 507
	5-25		10	3.84				8		
	5-31								3 2 0	

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TABLE I (CONTINUED)

OBSTRUCTIVE JAUNDICE											
No.	Date	Days of Jaundice	Index	Hippuric	Phos. Lipids	Cholesterol		Urob.	Bromsulph. Retention	Comment	
						Total	Ester %		2' 6' 15'		
46	6-6-39 6-13	77	170 160	Very low Very low	32.1	463	11				Cancer common duct and liver. Desired operation. Very poor peritonitis.
47	8-10-38 8-19 8-29 10-22 1-26-39 2-2-39 2-2-39	14	40 80 80 35 17	0.50 1.02 .88 1.01 2.88 2.90	17.2 12.9	287 235	42 45	32 32 32 8	(2-27-39) 100 80 40 (4-22-39) 20 0 0		Benign stricture com. duct. 2 operations, drainage of gall bladder and short circuit. Biopsy biliary cirrhosis. Recovery.
48	9-2-38	7	60-75	1.97	9.7	210	68	16			Cancer head of pancreas. Operation, death.
49	8-31-38	11	105	2.75	33.6	169	53	4-2			Cancer head of pancreas. Operation, death (cholelith?).
50	10-11-38	14	60	0.52	22.7	478	17				Terminal NPN 120.
51	8-22-39 4-27 4-6 7-27-38	90	90 100 100	1.82 1.35	20	380	23.4				Cancer liver, marked obstruction of ducts, secondary to cancer of stomach. Semi-comm. Died soon after admission. P.M.
52	7-29-38	75	18-15	2.48	20.8	243 268 293	33 35 45	0 0 0			Cancer head of pancreas. Refused operation 3 months before. Operation. Relief.
53	1-20-39 1-30 1-31 2-20 1-6-39 5-15	1	100+ 150 200 25	0.70 1.07 1.67	14.4	511	71	8			Partial obstruction from adhesion about common duct. Operation 9-10-38.
54	4-21-39 5-3	7	40-20	1.29 2.28	10.1	193	66	0 4			Cancer of liver and ducts secondary to cancer of rectum. Rapid downhill course, deep jaundice. Liver nodular. Death P.M.
55			40 60	0.5 1.77	24	335	50	64.5			Operation. Strains in common duct.
56					13.2 11.5	253 241	68 65				Gall bladder, common duct stone, operation. Diabetes mellitus. Slow recovery.
57											Cancer of head of pancreas. Progressive, obstructive jaundice. Left hospital against advice.
GALL BLADDER DISEASE (WITHOUT KNOWN OBSTRUCTION)											
No.	Date	Days of Jaundice	Index	Hippuric	Phos. Lipids	Cholesterol		Urob.	Bromsulph. Retention	Comment	
						Total	Ester %		2' 6' 15'		
58	2-21-38 2-10 3-22-39 3-26 4-5 4-13 4-27 5-23	3	18 12 18 75-70 110-70 10	1.54 2.80 2.45 1.53 2.24 2.41 1.10 1.31 2.18 1.40	11.6	284	67	128 30 16			First attack of mild jaundice rapid recovery. Normal liver function 5 mos. later. Graham +.
59	12-23-38	6 mos. Inter. mittent	50-10	1.40	13	139 200 182	37 50 64	8 8 16 256			Gall stones. Pancreatitis hepatitis. Bleeding tendency. Vitamin K used. Operation 6-10-39.
60	11-26-38 3-30-39 4-2	14	12-10 7	3.34 3.01	8.1	166	67	64-32			Recurrent attacks of jaundice. Graham +. Prior surgical risk.
61	11-2-38 11-10 10-8-38	Intermittently 6 yrs.	10 12 25-15	0.71 1.73 1.10	7 7.1	288 133 186	56 62 60	16 64 16			Gall stones. Giardiasis, cholecystectomy. Common duct empty.
62	5-2-39 7-16 6-6	4	80-40 60-18	1.48 3.23	8.3	186	61	32 64	30 20 0		Large solitary gall stone. Rapid recovery. Refused operation.
63	4-6-39 4-15 4-20 5-8	6 wks.	90 100+ 60 25	1.40 0.55 1.41 2.52	13.4 9.5	204 234 237	47 53 76	128 64			2 previous G. Bl. operations. Poor risk. Died coronary thrombosis.
64	4-7-39 4-15 5-8	1 day	60 40-15 8	1.39 2.46 3.68	53 11.3	125 98	64 61	0 269 64 128			Gall bladder, broncho-pneumonitis. Rapid convalescence.
65	6-1-39 7-12 6-14		20-80 25 20	Very low 1.05 1.80	14.4	100 170 157	64 63 69	64 128-16			Pancreatitis with walled off abscess in epigastrium. Operation.
66						178 141	33 48	64 128 64			Graham + after jaundice gone. Large solitary stone. Operation, rapid recovery.
67											Cholangitis ? pathologic gall bladder. Sulphanilamide used. Septic fever 4 weeks. Operation.

tween 253-478 mg. per 100 cc. (normal 150-220 mg.) and it was normal or only slightly decreased in the other chronic cases, i.e. cirrhosis, and gall bladder disease without obstruction of the common duct. In a few of the cases of acute hepatitis the values were moderately low during some period of the illness. The cholesterol ester percentage (normal 60-70%) was low in about 68% of the cases of acute hepatitis. One-half of these returned to normal upon improvement of the patient, the rest remained low during the

period of observation. The milder cases, 32 per cent, were always normal. There were two deaths in this group, both of which had a low ester percentage (34 per cent and 10 per cent). In the chronic cirrhoses, the percentage of ester cholesterol was low in 45 per cent of the cases. One-half of these returned to normal and the other half remained low. Almost twice as many chronic cases as acute were always normal. In five out of eight deaths in this group the percentage of ester was normal, or

In the gall bladder cases the hippuric test was normal in about 1/10 and low in about 9/10, less than 1/2 of the latter returned to normal. The fact that all the gall bladder cases were jaundiced may explain the high percentage of low hippuric tests on the basis of cholangitis, infection and liver cell damage.

In 22 cases *bromsulphalein* tests were made after the jaundice was gone. Retention of this dye ran

Number of Cases		Phos.-Lipids (8-10)		Total Choles. (150-220)			Ester-Per Cent (60-70)			Hippuric (2½-7)		
		%	%	%	%	%	%	%	%	%	%	
17	ACUTE HEPATITIS	Normal	+	Low	Normal	+	Normal	Low to	Low	Normal	Low to	Low
		81	19	38	38	24	28	36	36	12	76	12
								72			88	
21	CHRONIC CIRRHOSES	93	7	45	40	15	55	25	20		10	90
								45			100	
10	GALL BLADDER	50	50	11	67	22	55	34	11	11	34	53
								45			89	
4	TUMORS	80	20		100		100					100
11	OBSTRUCTION	10	90		18	82	19	9	72	18	10	72
								91			92	
3	HEMOLYTIC											
66	JAUNDICE	100		66	34		66	34		66	34	

Number of Cases		Phos.-Lipids (8-10)		Total Choles. (150-220)			Ester-Per Cent (60-70)			Hippuric (2½-7)		
		%			%			%			%	
		Normal	+	Low	Normal	+	Normal	Low to	Low	Normal	Low to	Low
17	ACUTE HEPATITIS	81	19	38	38	24	28	36	36	12	76	12
								72			88	
21	CHRONIC CIRRHOIS	93	7	45	40	15	55	25	20		10	90
								45			100	
10	GALL BLADDER	50	50	11	67	22	55	34	11	11	34	53
								45			89	
4	TUMORS	80	20		100		100					100
11	OBSTRUCTION	10	90		18	82	19	9	72	18	10	72
								91			92	
3	HEMOLYTIC											
66	JAUNDICE	100		66	34		66	34		66	34	

almost exactly parallel to lowered hippuric acid excretion. Very slow recovery of normal liver function took place in some cases requiring 6 or 8 months, and the order of recovery was approximately as follows: the ester per cent or the biliary index, later the hippuric acid and bromsulphalein excretion.

The Ivy bleeding time was measured in 27 cases and prolonged bleeding time by this method was commonly associated with poor liver function. In seven fatal cases in which the Ivy test was made, five had prolonged bleeding time (4, 4, 4, 6 and 20 minutes). In a few later cases the prothrombin time in the blood was used instead.

In this paper we have outlined the object of our study and the methods used, and have given in detail the results of the tests in the various diseases of the liver. A second paper will follow entitled "Clinical Value of the Tests" in which the clinical uses of the various tests for diagnosis and prognosis are outlined and compared.

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DISCUSSION

DR. ALBERT M. SNELL (Rochester, Minn.): I was much interested in Doctor White's remarks concerning the usefulness of the hippuric acid test. I think, taking everything into account, that it has given us more information about the general state of the hepatic parenchyma of the jaundiced patient than any other test that we have used. In the presence of jaundice we have found it of great prognostic value. So much so that our surgeons are reluctant to accept the risk of operating on patients whose hippuric acid synthesis is reduced by more than 50 per cent. Our experience with the cholesterol esters ratio has been definitely less satisfactory and we have been unable to correlate the observed changes with any constant clinical syndrome or pathologic change in the liver.

The Effects of Vitamin Deficiency on the Gastro-Intestinal Tract*

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THE relationship of the gastro-intestinal tract to states of vitamin deficiency is one of great importance for not only is the gastro-intestinal tract the normal portal of entry for vitamins but its structure and function may be significantly and vitally impaired by deficiencies of them. Two years ago Dr. Snell and I called to your attention the clinical importance of the first phase of this problem in a discussion of the role of alterations in gastro-intestinal function in setting the stage for the development of deficiency states. The present discussion deals with the other phase of this problem namely with the effects of vitamin deficiency on the gastro-intestinal tract.

Experience indicates that fundamentally the most significant roles of the gastro-intestinal tract in predisposing to or conditioning deficiency diseases have to do with an inadequate intake of food, with loss of essential secretions or of food itself, with a lack or decreased production of essential endogenous substances, with inadequate intestinal absorption and perhaps with impaired metabolic activity of certain of the digestive organs. Similarly experience indicates that most of these gastro-intestinal abnormalities may result from deficiency of one or more of the vitamins.

A recapitulation of these facts emphasizes some of the difficulties surrounding a solution of the problem of the effects of vitamin deficiency on the gastro-intestinal tract. In an individual case it may be extremely difficult if not impossible to state whether an alteration in gastro-intestinal function is primary or

whether it is secondary to a state of vitamin deficiency. Other difficulties which are encountered in any attempt to solve this problem are that in man, at least, almost all vitamin deficiency states are multiple; that is they are the result of deficiency of more than one of the vitamins. It is therefore very difficult to determine the effect of deficiency of a single vitamin on the gastro-intestinal function of man. In the third place many of the changes in the gastro-intestinal tract which have been ascribed to vitamin deficiency are non-specific and occur in a large variety of conditions. Many of the observations which have been reported have been based on experiments in animals, on indirect evidence, on symptomatic changes or on therapeutic responses, none of which are entirely satisfactory in clarifying the issue.

Although the problem is one which is difficult to solve it also is one of great importance because many persons subsist on a diet which is borderline in adequacy of various vitamins and particularly of components of the Vitamin B complex. The vicious cycle which may be formed when there is either vitamin deficiency or gastro-intestinal disease may be one of sufficient degree to produce a state of marked vitamin deficiency or it may cause a patient who otherwise would be reasonably well to be precipitated into a state of vitamin deficiency of mild or moderate degree.

Finally the importance of recognizing and understanding this problem lies principally in the fact that vitamin deficiency states are an unusual group of diseases in the respect that they can be entirely prevented

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and that with the exceptions of a few extreme instances they are completely amenable to cure.

The early symptoms of nutritional deficiency are vague and according to Minot (2) a sense of fatigue or lack of energy is common and inefficiency and mental irritability, mild anemia and simple disorders of the digestive tract usually are present.

Haden (3) has classified the lesions of the alimentary tract which are observed as manifestations of deficiency diseases as follows: "(1) anorexia (2) stomatitis (3) glossitis (4) atrophy of tongue (5) achlorhydria (6) loss of specific ferments (7) diarrhea (8) loss of tone of gastro-intestinal tract (9) ulceration of intestine." Other reports of the gastro-intestinal manifestation of deficiency disease which have been made by a number of observers are noted in the subsequent discussion.

PRESENT STUDY

The present study deals with the effects of vitamin deficiency on the gastro-intestinal tract and consists of a summary of available information on this phase of deficiency diseases with some observations in cases in which gastro-intestinal manifestations were a prominent feature. For purposes of a clearer understanding the material has been grouped into sections on the effects of deficiency of each vitamin and the abnormalities associated with deficiency of each vitamin have been grouped into those which are symptomatic, those which produce physiologic changes and those which result in pathologic changes.

THE EFFECT OF DEFICIENCY OF VITAMIN A

Vitamin A is essential for the normal function and integrity of the epithelial tissues of the animal organism. The characteristic changes which follow deficiency of this vitamin have to do with atrophy of the epithelium concerned, the substitution for it of a stratified keratinizing epithelium, followed in many cases by secondary infection of the tissues.

Pathologic changes. In animals. A variety of changes and an absence of changes have been described in the gastro-intestinal tract of Vitamin A deficient animals; they recently have been summarized by Robertson (4). Richards (5) reports that in rats the earliest macroscopic sign of Vitamin A deficiency is in the epithelial lining of the digestive tract which reveals signs of inflammation, hemorrhagic areas and at times ulceration of the stomach. Manville (6) and Cox (7) have reported similar changes in the stomach of rats on a diet deficient in Vitamin A. Wolbach (8) states that in animals with experimental Vitamin A deficiency the mucosa of the stomach and intestines show practically no change and that when changes occur they consist of atrophy which progresses to a state wherein the cells although having the appearance of viability become inert in physiologic activities and in their roles of covering membrane. Changes in the small and large intestine which have been described include atrophy of Brunner's glands, atrophy of the mucous glands, disappearance of goblet cells, chronic inflammatory and proliferative changes, hemorrhagic phenomena and ulceration.

Wolbach and Howe (9) have noted atrophy of the pancreas of the rat in Vitamin A deficiency. Changes which have been noted in the liver include atrophy (Pillat and Chang) (10), hemosiderosis (Wolbach (11), and Sweet and K'ang) (12) and diminution in

size owing to decrease in amount of stored fat and glycogen (Wolbach and Howe (9), Bauercisen) (13).

In man. (Table I). There are surprisingly few reports of pathologic changes in the alimentary tract in cases of Vitamin A deficiency. McCarrison (14) emphasized the occurrence of infections and ulcerations in the gastro-intestinal tract in vitamin deficiency states. However in patients and animals he studied there were deficiencies of other vitamins than of A. In the case of Vitamin A deficiency in an infant reported by Wilson and Dubois (15) no noteworthy abnormality was found in the stomach, pylorus, duodenum, ileum or colon. In the pancreas there were marked changes consisting of inflammation, fibrosis and numerous epithelial-lined cyst-like cavities which apparently were dilated acini. Schiodt (16), Singh (17) and Keefer (18) have reported that atrophy of

TABLE I
Gastro-intestinal manifestations of Vitamin A deficiency

Type of Change	Manifestation	
	Usual	Occasional
Symptomatic	None	Diarrhea
Physiologic	None	Hypochlorhydria Achlorhydria Interference with absorption?
Pathologic	None	1. Atrophy or inflammation of oral, gastric and intestinal mucosa. 2. Atrophy, fibrosis, cyst formation and inflammation of accessory glandular organs. 3. Atrophy, fibrosis, hemosiderosis of liver? 4. Absence or defective enamel and dentine formation of teeth.

the mucosa of the intestinal tract and gastro-enteritis and colitis occur in man in cases of Vitamin A deficiency.

Sweet and K'ang (12) who have had extensive clinical experience with Vitamin A deficiency state in a report of autopsies on seventeen Chinese patients with Vitamin A deficiency, that in five of them the esophagus showed hyperkeratosis and that the digestive tract in all of the cases (17) otherwise was normal. Pathologic changes in the liver of patients with Vitamin A deficiency have not been reported although Wolbach (11) mentions the possibility of hemosiderosis of the liver as a manifestation of deficiency of this vitamin.

Physiologic changes. In animals. Steenbock and his associates (19) have reported that Vitamin A deficiency interferes with the absorption of fat from the intestine of the rat while Kik, Sure and Buchanan (20) note that in rats there is an appreciable decrease in hepatic lipase in this condition.

In man. Reduction in the hydrochloric acid content of the gastric juice in Vitamin A deficiency has been noted by Stepp (21), Boiler (22) and Will (23). Pillat and Chang (10) observed achlorhydria in four of fifteen cases of Vitamin A deficiency following stimu-

lation with histamine. In ten of the cases there was definite depression of gastric secretion. Since achlorhydria is rare in the Chinese they considered the findings to be significant. The latter observers reported further that the degree of impairment of gastric function seemed to be related to the duration and severity of the disease of the eye (xerophthalmia) and that the achlorhydria improved when Vitamin A was administered.

Stepp (21) also suggested that Vitamin A deficiency may lead to interference with intestinal absorption in man.

Symptomatic changes. The only gastro-intestinal symptom which has been noted with any frequency in Vitamin A deficiency is diarrhea. Apparently this is not an uncommon accompaniment of xerophthalmia as noted by Stepp (21), Nicholls (24) and Pillat (25). This symptom also has been noted in Vitamin A deficiency in mice, cows and monkeys.

Comment. The paucity of gastro-intestinal symptoms and pathologic changes in cases of Vitamin A deficiency in man is surprising in view of the fact that a large part of the gastro-intestinal tract is made up of epithelial tissue. Since patients with marked degrees of Vitamin A deficiency are observed extremely uncommonly in the United States and since changes in the gastro-intestinal tract do not commonly accompany mild degrees of Vitamin A deficiency clinicians and physiologists in the future probably will not find significant gastro-intestinal alterations in most cases of Vitamin A deficiency which come under their observation. Patients exhibiting such symptoms or lesions have not been observed by me.

Observations which have been made to date suggest that the most likely types of pathologic changes in the gastro-intestinal tract to be expected in Vitamin A deficiency are alterations in the teeth, atrophy or inflammatory changes in the mucosa of the mouth, stomach and intestine and atrophy, cyst formation or inflammation of accessory glandular organs such as the salivary glands, the pancreas and the liver. These changes may interfere with absorption from the intestine, may lead to hypochlorhydria or to achlorhydria or symptomatically may lead to diarrhea. The cause for the diarrhea is not clear. It seems most likely to be related to atrophic or inflammatory changes in the mucosa of the large or small intestine or perhaps to achlorhydria although as noted previously in many cases of keratolmalacia the gastro-intestinal tract has appeared to be normal at postmortem examination.

There has been much discussion of the relation of the liver to Vitamin A deficiency. Since the liver is the chief storehouse for Vitamin A it is not surprising that in cases of hepatic disease the Vitamin A content of the liver is diminished or that the vitamin may be absent from it as noted by Moore (26). Haig, Hecht and Patch (27) have indicated that in cases of alcoholic cirrhosis evidence of Vitamin A deficiency is very common. However in cirrhosis and other forms of chronic hepatic disease and in various abnormalities of the gastro-intestinal tract, if deficiency of Vitamin A occurs it seems much more likely that it is secondary to a deficiency in intake, absorption, storage or metabolism of the vitamin rather than primarily the cause of the hepatic or gastro-intestinal disease.

A possible role for Vitamin A deficiency in gastric and duodenal ulcer was suggested by McCarrison (14, 28) and has been confirmed and denied by other

workers. While minute ulcers occur in the stomach of the Vitamin A deficient rat in some cases, convincing evidence that Vitamin A deficiency is related to peptic ulcer in man has not been produced. Indeed it seems quite unlikely that such evidence will be produced because the lesions have not been found in patients with severe Vitamin A deficiency, because most patients with peptic ulcer in this country at least, have an adequate intake of Vitamin A in the diet (milk, cream and butter) and because Vitamin A deficiency frequently leads to hypochlorhydria and achlorhydria. It seems most likely that when deficiency of Vitamin A occurs in association with peptic ulcer that the association is a coincidental one.

THE EFFECT OF DEFICIENCY OF VITAMIN B

Vitamin B has been found to consist of at least four and probably more distinct components. The known components are thiamin chloride, nicotinic acid, riboflavin and Vitamin B₆. As yet sufficient time has not elapsed clearly to distinguish the effects of the individual components on gastro-intestinal function. Consequently in the subsequent discussion mention will be made of the effect of deficiencies of the Vitamin B complex unless there is a reference to a specific component of the complex.

Pathologic changes. In animals. A large variety of pathologic changes in the gastro-intestinal tract of animals on diets deficient in Vitamin B have been reported. Summaries of these findings have been made by Schiodt (16), by Eddy and Dalldorf (29) and by others. In essence the changes consist of atrophy of the lingual papillae, glossitis and stomatitis, diffuse or localized areas of inflammatory disease in the stomach and intestinal tract, atrophy of the intestinal wall (including mucosal and muscle layers) erosion and ulceration particularly of the stomach but also of the intestine, hemorrhage into the stomach or intestine, degeneration of Auerbach's plexus, as well as other less important changes.

In man. (Table II). *Glossitis. Stomatitis.* Glossitis and stomatitis seem to be an integral part of pellagra, of pernicious anemia and of sprue. In pellagra, in the early stages the most common finding is a reddening of the papillae of the anterior third and tip of the tongue. There may be gradual extension of this process to involve the entire tongue and the buccal mucous membrane with characteristic appearances of a brick or fiery red color and of edema of the tongue which is revealed by marks of the teeth upon it. Associated with this there may be small aphthous ulcers located especially on the base of the tongue and on the buccal mucous membrane. These ulcers usually are covered by a yellowish or white membrane from which Vincent's organisms may be recovered. Often pain of a mild or severe character is associated with the glossitis. In sprue and in pernicious anemia the glossitis most commonly consists of diffuse atrophy of the papillae of the tongue which may or may not be preceded by or associated with some redness and soreness of the tongue and buccal mucous membranes. Somewhat similar changes in the tongue are to be noted in some cases of achlorhydric anemia, anemia of pregnancy, Plummer-Vinson syndrome, in malnutrition attended by dysentery and anemia, intestinal strictures, dibothriocephalus latus infestation and achlorhydria according to Hutter, Middleton and

Steenbock (30). It is quite likely that all of these changes are the result of deficiency of components of the Vitamin B complex or substances closely related to them.

Stomach and Intestine. There is very little clear cut evidence of the pathologic changes in the stomach and intestine in cases of deficiency of Vitamin B. Evidence of the paucity of our knowledge of this subject is indicated by the fact that in a recent article in which he reviewed the pathology of beriberi, Vedder (31) who has had wide experience with this disease fails to mention any gastro-intestinal abnormalities in beriberi. Stepp (21) reports that there is a peculiar tendency to inflammatory reaction in the intestine of patients with Vitamin B deficiency while McCarrison

liver apparently are principally secondary to the associated circulatory failure. Vedder (31) mentions that the liver often has the typical nutmeg character and that some degree of cloudy swelling or fatty degeneration may be found in the liver.

Physiologic changes. In man. (Table II). The outstanding physiologic abnormalities associated with deficiency of Vitamin B may be grouped under the headings of secretory, motor and absorptive disturbances.

Interference with the secretion of hydrochloric acid seems to be a significant change in many cases of pellagra and in other syndromes apparently due to deficiency of the vitamin. Achlorhydria following stimulation with histamine is present in about fifty to sixty-five per cent of cases of pellagra. It occurs also in some cases of beriberi although Kitamura and Shimazono (32) and Keefer (33) are of the opinion that achlorhydria is not associated with this disease. In a study of the gastric acidity of alcohol addicts many of whom exhibited evidence of deficiency states, Joffe and Jolliffe (34) report that in the "uncomplicated" subjects, in polyneuritics and in pellagrins the incidence of achlorhydria was fifteen, twenty-nine and fifty-two per cent respectively. In fact Joffe and Jolliffe (34) have gone so far as to suggest that an achlorhydria preventive factor not identical with Vitamin B₁ probably is present in the Vitamin B complex.

Changes in the secretion of other digestive juices has not been noted in man but Kik, Sure and Buchanan (20) have observed a marked decrease in the digestive efficiency of pancreatic esterase and moderate decrease in the concentration of pancreatic and hepatic lipase in Vitamin B₁ deficiency in the rat.

One of the most interesting although as yet unexplained phases of Vitamin B deficiency is that having to do with the motor activity of the intestine in diseases due to deficiency of Vitamin B or of closely related substances. Observations of the changes have been made principally by roentgenologic methods although a few studies have been reported following insertion of balloons through intestinal fistulas. The changes which have been observed in sprue, in beriberi, in pellagra and in chronic ulcerative colitis are non-specific and consist in essence of distortion of the mucosal pattern and of a variation in the caliber of the intestinal loops.

Mackie and Pound (35), and Snell and Camp (36) as well as others have discussed in detail the roentgenologic appearance of these abnormalities. In some cases the duodenum was dilated and the mucosal markings were thickened. Lower down in the intestinal tract there was a definite smoothing out of the irregular shadows of the valvulae conniventes and clumping of the barium in smooth sausage-like masses. Motility of the barium was considerably interfered with in some cases while in other ones the rapidity of passage of the barium meal was greater than the normal.

Considerable evidence has been presented to suggest that there are disturbances in absorption in cases of Vitamin B deficiency and "related" diseases of the small intestine. Interference with the absorption of fat in cases of sprue has been reported by Barker and Rhoads (37) and other investigators. Abnormalities in absorption of essential hematopoietic substances in similar types of cases also has been suggested. All of this evidence is indirect, however, and only recently has Groen (38) produced more direct evidence that in

TABLE II

Gastro-intestinal alterations in Vitamin B deficiency

Type of Change	Factor	Manifestation
Symptomatic	B ₁	Anorexia
	Nicotinic acid	Diarrhea, sore mouth
	Other?	Constipation, dysphagia, flatulence vomiting? Other vague symptoms
Physiologic	B ₁	Deficient absorption of glucose Achlorhydria? Alteration in muscle tone?
	Nicotinic acid	Achlorhydria? Alteration in muscle tone?
	Other?	Alteration in muscle tone? Achlorhydria? Deficient absorption of glucose and fat
Pathologic	B ₁	Atrophy and inflammation of mucosa?
	Nicotinic acid	Atrophy and inflammation of mucosa? Glossitis, stomatitis, proctitis
	Other?	Atrophy and inflammation of mucosa? Stomatitis?

Other changes which it has been suggested occur in Vitamin B deficiency:

1. Degeneration of Auerbach's plexus
2. Hepatic disease—cirrhosis
3. Peculiar tendency to inflammatory reactions.

(14) in his early observations noted degeneration of Auerbach's plexus in cases of Vitamin B deficiency. Roentgenologic examination of the small intestine of some of these patients suggests the occurrence of edema of the mucosa but whether these changes are characteristic of deficiency of Vitamin B is not clear. Acute inflammatory reactions in the mucosa of the rectum and sigmoid are often to be observed in cases of pellagra.

In addition to the above evidence there are numerous reports of the occurrence of peptic ulcer, of ulcerative colitis and of vague and indefinite types of atrophy and inflammation of the intestinal tract in Vitamin B deficiency.

Pancreas and Liver. In beriberi the pancreas is reported at times to be shrunken and even slightly fibrotic and the islands of Langerhans to be either not affected or hypertrophic. Changes to be noted in the

pernicious anemia, nontropical sprue, "alcoholic" polyneuritis with pellagra there is diminished absorption of glucose as measured quantitatively by means of intubation of the intestine and isolation of a segment of it by means of inflated balloons. Improvement in function with return to a normal condition followed parenteral administration of liver extract in these cases.

The effect of Vitamin B on the liver is not certain. The occurrence of cirrhosis in chronic alcohol addicts with or without accompanying signs of Vitamin B deficiency has suggested to some clinicians the possibility that cirrhosis might be due to deficiency of Vitamin B. Direct evidence to substantiate this opinion has not been presented however. In animals with experimental Vitamin B deficiency atrophy of the liver is said to occur.

Symptoms. In man. (Table II). A large number of gastro-intestinal symptoms including anorexia, constipation, diarrhea, dysphagia, flatulence and vomiting have been ascribed to deficiency of components of the Vitamin B complex. Of these symptoms it seems clearly established that *anorexia* accompanies deficiency of Vitamin B₁ in man as well as in animals. Cowgill (39) and other observers have produced evidence that anorexia is a very early manifestation of Vitamin B₁ deficiency and the studies of Schlutz and Knott (40) indicate that the intake of Vitamin B related to the appetite of children. *Diarrhea* is another very common symptom of Vitamin B deficiency. It occurs in pellagra and beriberi in both of which conditions the occurrence of diarrhea has raised the question as to whether or not it led to the development of the deficiency disease or whether the diarrhea was the result of it or both. There is insufficient evidence at the present time to explain other symptoms such as constipation, flatulence, dysphagia and vomiting on the basis of Vitamin B deficiency when they exist without other more definite evidence of deficiency of components of the Vitamin B complex.

Comment. It seems quite clear that thiamin and nicotinic acid are essential for normal functioning of the gastro-intestinal tract. Of the pathologic and physiologic changes and symptoms in deficiency of Vitamin B which have been observed, anorexia apparently is the only one which clearly is related to deficiency of Vitamin B₁. Indeed Strauss (41) recently has pointed out, there is considerable evidence to support the contention that changes in gastro-intestinal tract such as glossitis, achlorhydria and diarrhea are at least in part if not entirely manifestations of deficiency of some portion of the Vitamin B complex other than thiamin. The glossitis, diarrhea, and proctitis of pellagra seem very closely related to deficiency of nicotinic acid for they respond dramatically within a few hours or days to administration of this substance.

It is not clear as yet what factor or factors in liver extract have to do with the changes in the motility and tonus of the intestine and with the interference in absorption of glucose and of fat in patients with sprue, with peripheral neuritis of the alcoholic type, with pernicious anemia and with related conditions. In general these changes in the intestine vary with the intensity of the disease. The relation of them at least in part to deficiency of Vitamin B is suggested by occurrence of them in the above noted conditions

and improvement of them following administration of components of the Vitamin B complex and particularly of liver extract. That other factors such as a deficiency of protein may be significant is suggested by the observations of Ravdin and his associates (63) who recently have demonstrated that changes in intestinal as well as in gastric motility in dogs and patients accompany low values for serum protein.

The mechanism by which deficiency of Vitamin B may lead to the symptomatic and physiologic disturbance is not clear. As Williams and Spies (42) have stated "at the present time it is difficult to understand how an inadequate amount of this Vitamin (B₁) predisposes to gastro-intestinal disturbances." The cause for the anorexia accompanying Vitamin B deficiency is that it is a result of atrophy or inflammation of the gastric mucosa. Proof is lacking that interference of intestinal motor activity is the result of degeneration of Auerbach's plexus as McCarrison (14) suggested years ago. Interference with absorption may result from atrophy or inflammatory changes in the intestinal mucosa, changes which apparently are reversible in the majority of cases. The cause of the diarrhea of pellagra is not clear but the dramatic response of nicotinic acid in stopping it suggests the possibility that whatever the pathologic changes causing it may be, they are readily reversible ones.

There are a number of observers who believe that lack of Vitamin B may produce peptic ulcer in man, but there is very little evidence in favor of this view. Mackie and Pound (35) have demonstrated roentgenologic changes in the small intestine in many cases of chronic ulcerative colitis. They have suggested that these changes in the small intestine are related to the deficiency states which are observed by them in cases of chronic ulcerative colitis and perhaps that they played a role as a conditioning factor in development of them. The relation of these changes to chronic ulcerative colitis is not entirely clear.

THE EFFECTS OF DEFICIENCY OF VITAMIN C

The gastro-intestinal tract seems to be spared in deficiency of Vitamin C with the exception of changes in the gums which are characteristic of scurvy and of gastro-intestinal hemorrhages which occasionally occur.

Pathologic changes. In animals. Pathologic changes in animals with experimental scurvy include abnormalities in the teeth, gingivitis, hemorrhage into the gastric and intestinal mucosa, ulceration of the stomach and intestine, congestion with patches of degeneration of the islets of Langerhans and fatty infiltration of the liver, (Bessey, Menten and King) (43). Gastric and duodenal ulcers are reported to occur with great frequency in guinea pigs on a diet without Vitamin C according to Holst and Frolich (44), McCarrison (45), Magee, Anderson and McCallum (46) and Smith and McConkey (47).

In man. (Table III). Pathologic changes in the gastro-intestinal tract of man in scurvy appear to be limited to the mouth and consist of mild or severe gingivitis. Oozing of blood with hematemesis or melena have been described in cases of scurvy in man and presumably they occur from small lesions in the mucosa of the stomach and intestine. Peptic ulcer

not an accompaniment of scurvy. Musser and Sodeman (48) recently observed very severe proctitis in a patient with Vitamin C deficiency.

Physiologic effects. In animals. According to Einhauser (49) Vitamin C is a normal constituent of the wall of the intestine and serves a detoxifying and protecting function. Shimamura (50) reports that in guinea pigs on a scorbutic diet the glycogen content of the liver is low and that it would be increased up to but not beyond a certain level by daily administration of Vitamin C. In a study of the motility and permeability of the intestine by means of a variety of different methods Smith (64) could find no significant impairment in acute or chronic scurvy.

In man. There is very little evidence of physiologic impairment of the gastro-intestinal tract in scurvy in man. Coffé and Dulee (51) have reported that in normal subjects intravenous administration of Vitamin C increased the volume and the concentration of free hydrochloric acid and of total acid in the gastric con-

TABLE III

The gastro-intestinal alterations in Vitamin C deficiency

Type of Change	Manifestation	
	Usual	Occasional
Symptomatic	Gingivitis Anorexia	Diarrhea Hemorrhage
Physiologic	None noted	None noted
Pathologic	Infected, spongy, bleeding gums	Dental caries Intestinal hemorrhage

tent although it had no such effect in a case of pernicious anemia. Absorption of glucose from the small intestine of two patients with scurvy was found to be normal by Groen (38).

Symptoms. The outstanding gastro-intestinal symptoms in scurvy are related to gingivitis. Anorexia and diarrhea may be present; occasionally there may be some gross bleeding.

Comment. Although Vitamin C apparently is essential for all living cells, there is very little evidence of significant gastro-intestinal alterations in Vitamin C deficiency with the exception of gingivitis and perhaps occasionally of bleeding. However a great deal of controversy has surrounded the possible role of Vitamin C deficiency in cases of peptic ulcer and in bleeding from ulcer and other lesions. Numerous reports in the literature have pointed to the occurrence of ulcers having some of the characteristics of peptic ulcer in the stomach and duodenum and intestine of animals with experimental scurvy and there has been repeated confirmation of the observation that low values for Vitamin C in the blood are the rule for patients with peptic ulcer. The studies of Ingalls and Warren (52), Bourne (53), and Rivers and Carlson (54) agree that patients with peptic ulcer, even those who may be receiving an approved diet for ulcer, have lower levels of ascorbic acid in the blood and urine than have normal persons. Elder and Emery (55) have analyzed the eating habits of twenty-five patients with ulcer and of twenty-five control patients and have come to

the conclusion that peptic ulcer is not a deficiency disease in the sense in which this term ordinarily is used. Despite all of these findings there is considerable doubt in the minds of many clinicians as to the relation of deficiency of Vitamin C to peptic ulcer and certainly further studies will be required to settle this point. It seems quite reasonable to agree with Jones and his collaborators (56) that it is highly probable that the findings just noted represent the results of a deficiency secondary to the original ulcer condition, rather than that there is a causative relation to the formation of ulcer.

The relation of hemorrhage from the gastro-intestinal tract to deficiency of Vitamin C remains unsettled. The observations of Portnoy and Wilkinson (57) indicate that patients who have peptic ulcer and bleed from them and especially those who have hematemesis have marked Vitamin C deficiency—in fact such cases usually present more evidence of Vitamin C deficiency than do patients with peptic ulcer who have not bled. The likelihood that this result is secondary to a diet deficient in Vitamin C is great but further evidence will be required before this point can be settled definitely.

THE EFFECT OF DEFICIENCY OF VITAMIN D

Although diseases of the mucosa of the small intestine and interference with the flow of bile into the duodenum may seriously impair absorption of Vitamin D and although the liver appears to be essential for the anti-rachitic efficiency of Vitamin D in animals there is very little if any evidence that deficiency of Vitamin D leads to impairment in gastro-intestinal function or structure. Atony of the intestine has been described as an accompaniment of rickets but the relation of it to deficiency of Vitamin D is not clear. Yoder (58) has produced evidence from experiments on rats which he feels indicates that "there must be a minimal requirement of Vitamin D by the digestive tract for a tonicity which can maintain either a decreased intestinal volume or increased motility."

THE EFFECT OF DEFICIENCY OF VITAMIN E

Evidence is lacking that deficiency of Vitamin E results in significant gastro-intestinal abnormalities.

THE EFFECT OF DEFICIENCY OF VITAMIN K

Considerable evidence has accumulated to indicate that there is a relation between deficiency of Vitamin K and the hemorrhagic tendency in jaundice. In cases of Vitamin K deficiency in chicks and perhaps also in other animals and in man there is a deficiency of prothrombin in the blood plasma. This effect may be brought about by a variety of mechanisms including a diet deficient in Vitamin K, interference with absorption of the vitamin because of absence of bile in the intestine, or as a result of hepatic damage with impairment in the fabrication, storage or activation of prothrombin which seems to occur in the liver. Evidence has not been presented to suggest that any abnormality in gastro-intestinal function or structure occurs as a result of Vitamin K deficiency with the exception of those changes associated with bleeding.

THE EFFECTS OF DEFICIENCY OF ANTI-GIZZARD EROSION FACTOR

In his original studies of the hemorrhagic disease of chicks, Dam (59) reported the occurrence of erosion

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DISCUSSION

DR. MARTIN G. VORHAUS (New York): There is no question that a paper on this subject is timely before this group particularly in regard to the question of symptoms of deficiency states. As Dr. Wilbur has shown, one of the most important in the group is the symptom of anorexia. All experimenters in the vitamin field agree that in B deficiency anorexia is an outstanding manifestation, but, unfortunately, the clinician has taken the point of view that the administration of the B group is an excellent method of combating this symptom.

In our clinical experience we have found that the reverse is true. We have been able to stimulate appetite in less than 15 per cent of cases who have received thiamin in large doses over a long period of time. It is important to stress this point since a great deal has been written upon the value of thiamin in the treatment of anorexia, and the clinician who accepts these facts is bound to find that his clinical experience is extremely disappointing.

The same thing is true in consideration of constipation. Though it is frequently present in animals, less than 1 per cent (and a great deal less than 1 per cent) of the cases of constipation are improved by administration of the Vitamin B complex.

The Clinical Value of Quantitative Vitamin Determinations*

By

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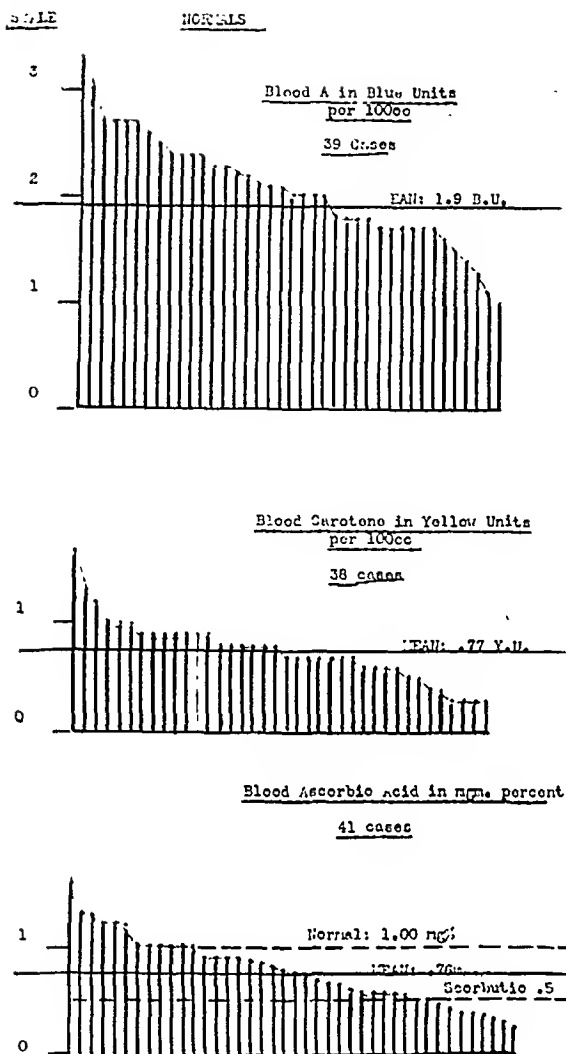
NEW YORK, NEW YORK

THE rapid increase in knowledge of the chemistry of the vitamins has given new impetus to studies of nutrition. Quantitative chemical and physical methods are being developed which are applicable to clinical practice. These have greatly broadened the scope of the field. While the disease states resulting from extreme deprivation of certain vitamins have long been recognized, we have had no means to explore border-line conditions nor indeed to recognize them.

*From the Gray Laboratory of the Roosevelt Hospital. Read at the Annual 1939 Session of the American Gastro-Enterological Association at Atlantic City.

They constitute a field of medicine which is almost wholly unexplored.

The experimental pathology of the avitaminoses when correlated with observed human pathology indicate the fundamental importance of adequate supplies of these essential food factors. Dalldorf and Eddy (1) have presented a critical evaluation of this evidence. These structural changes inevitably are accompanied by disturbances of normal physiology—affecting many organs. The physical signs and symptoms at present associated with the avitaminoses are indicative of



Graph 1

severe grades of deficiency. It is assumed that the individual who presents none of these phenomena is in a satisfactory state of nutrition. This is not necessarily the case. Less advanced grades of vitamin deficiency lacking characteristic signs and symptoms unquestionably pass unrecognized. It is not permissible to conclude from the type of negative evidence so far available, that the lesser degrees of deficiency do not militate against optimum health on the one hand, and contribute to disease on the other.

The exact requirements for the particular vitamins are unknown. The estimated requirements are based upon amounts apparently sufficient to protect against deficiency disease supplemented to provide a factor of safety. These values at best are only approximations. They are not valid criteria of adequacy especially in the presence of clinical conditions associated with faulty digestion, defective absorption from the intestinal tract, liver disease, or excessive metabolic requirements. It is evident that great variation in individual needs must occur. It is likewise evident that rational

and successful therapy must be based upon accurate standards of normal vitamin saturation, and upon direct quantitative methods which can be used for clinical investigation. Such tests are being developed, and although imperfect they afford a preliminary technique for exploration of deficiencies of Vitamin A; pro-Vitamin A, carotene; Vitamin C, and Vitamin K.

There is a paucity of literature dealing with blood values of Vitamin A. Menken (2) has reported the equivalent of 0 to 8.4 Lovibond blue units per 100 cc. Other reports which attempt to translate the colorimetric readings into terms of vitamin units are not comparable.

Data on blood carotene values are more numerous but show marked variation. Clausen (3) reported a fairly constant level at 0.08 mg. per 100 cc., the equivalent of 1.3 Lovibond yellow units, in normal children over two years of age.

Normal blood values for Vitamin C have been fairly well established by reports from many laboratories. Abt and Farmer (4) in a recent critical review, state that healthy persons taking what is considered to be an adequate intake of Vitamin C yield plasma values of 0.7 mgs. per 100 cc. or higher. Values below this level they consider subnormal, or at least suboptimal. According to them active scurvy may occur with a Vitamin C level up to 0.4 to 0.5 mgs. per 100 cc.

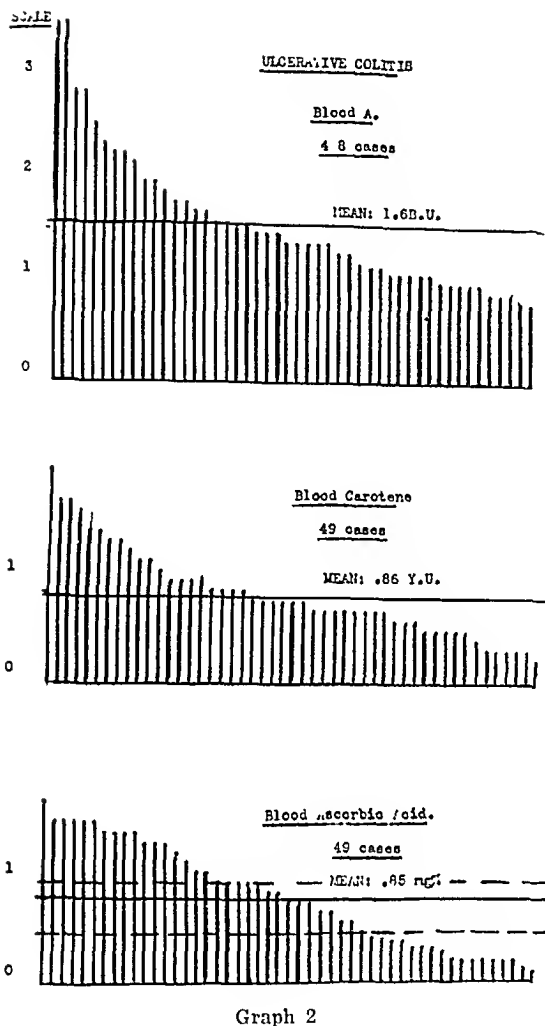
An additional antihemorrhagic dietary factor, Vitamin K originally described by Dam (5) has recently received much attention. Lack of this substance is associated with deficiency of prothrombin in the plasma of chicks with hemorrhagic disease, and of dogs and of man with various pathologic conditions of the biliary tract and the liver. Snell, Butt and Osterberg (6) have shown that oral administration of this fat soluble factor in the presence of adequate amounts of bile salts will increase the concentration of prothrombin and thereby reduce the clotting time of the blood. They have likewise shown that determination of prothrombin time may be used as an index of prothrombin concentration and indirectly, therefore, a measurement of Vitamin K deficiency.

MATERIAL

We have been impressed with the importance of mixed deficiency states occurring in the course of certain diseases, notably chronic ulcerative colitis and sprue (7, 8, 9). During the past year determinations of blood carotene, Vitamin A, Vitamin C and Vitamin K have been included among the routine studies of a considerable group of individuals. This report is based upon our findings in forty-one apparently normal healthy adults and two hundred and sixteen patients seen in hospital, dispensary, and private practice in New York City. The patient group includes forty-nine cases of chronic ulcerative colitis, forty-six cases of peptic ulcer, and one hundred and twenty-one miscellaneous ward cases.

METHODS

Plasma Vitamin A determinations have been done by the modification of Van Eckelan's method described by Menken (2). Readings are made against the blue plates of the Lovibond tintometer. Since the color reaction is transitory and since no completely satisfactory conversion factor for translation into units of



Graph 2

Vitamin A is available, results are expressed as Lovibond Blue Units (LBU).

The carotene determinations have been made by the same technique, by extraction and comparison with the yellow standards of the Lovibond Tintometer. It has seemed desirable to express results in terms of Lovibond Yellow Units (LYU) rather than to translate them into milligrams of carotene by reference to the Ferguson (10) curve.

Vitamin C determinations have been made by the method of Farmer and Abt (11). Results are expressed in terms of milligrams per 100 cc.

The Vitamin K status has been estimated by measurements of prothrombin time using the methods of Quick, Stanley-Brown and Bancroft (12) and of Quick (13). Results are expressed in seconds. The upper limit of normal for these methods is thirty seconds and fifteen seconds respectively.

FINDINGS IN NORMAL ADULTS

Forty-one apparently normal healthy adults were studied to calibrate the methods, and to establish normal ranges for purposes of comparison. Blood Vitamin C determinations were done on all, Vitamin

A in thirty-nine, and carotene in thirty-eight. Casual non-fasting determinations were made on each individual and subsequently the tests were repeated using morning fasting blood from each subject. The casual specimens revealed higher average values for each substance tested, larger ranges, and larger standard

TABLE I
Fasting normals

Vitamins Tested	Vitamin A	Carotene	Vitamin C
No Cases	39	38	41
Ave Finding	1.9 Blue units	0.77 Yellow units	0.76 mg. %
Range	2.3—1.0	1.7—0.3	1.60—0.25
St. Deviation	0.55	0.29	0.32
St. Deviation Means	0.08	0.04	0.05
Probable Error	0.05	0.03	0.03

deviations. Consequently the fasting values have been accepted as more significant and have been utilized throughout.

The thirty-nine normals tested gave an average Vitamin A content equivalent to 1.9 LBU with a standard deviation of ± 0.55 . The extremes were 1.0 LBU and 3.3 LBU. (Graph 1).

The blood carotene content in the thirty-eight normals averaged 0.77 LYU with a standard deviation of ± 0.29 . The extremes were 0.3 and 1.7 LYU.

The Vitamin C values in forty-one normals averaged 0.76 mgs. per 100 cc. with a standard deviation of 0.32. The extremes were 0.25 mgs. per 100 cc. and 1.60 mgs. per 100 cc.

ULCERATIVE COLITIS

Forty-nine cases of chronic ulcerative colitis have been studied in similar fashion. (Graph 2). The average Vitamin A value was found to be equivalent to 1.6 LBU; the standard deviation ± 0.67 , and the range 0.8 LBU to 3.6 LBU. Contrasting these findings

TABLE II
Ulcerative colitis cases

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No Cases	48	43	49
Ave Finding	1.6 Blue units	0.86 Yellow units	0.85 mg. %
Range	3.6—0.8	2.1—0.2	1.8—0.1
St. Deviation	0.67	0.41	0.33
St. Deviation Means	0.10	0.06	0.08
Probable Error	0.06	0.04	0.05

with those in the normal control group, the average is somewhat lower, the range is greater, and the lowest value observed is lower than any in the normal group. The average carotene content, 0.86 LYU is somewhat above that observed in the control group, the range is greater, the standard deviation is larger, and the lowest value is below that observed in normals. The average Vitamin C content, 0.85 mgs. per 100 cc. is likewise above the average value observed in the

normal group, the range is greater, the standard deviation larger, and the lowest value below that found in the controls.

Forty-six cases of peptic ulcer have been studied by the same technique. (Graph 3). All were hospitalized for treatment. The observations to be presented represent the first determinations after admission to the

TABLE III
Ulcer cases

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	46	46	43
Ave. Finding	1.5 Blue units	0.87 Yellow units	0.51 mg. %
Range	2.5 — 0.7	2.3 — 0.2	1.60 — 0.1
St. Deviation	0.45	0.40	0.13
St. Deviation Means	0.07	0.06	0.02
Probable Error	0.04	0.04	0.01

wards. The average Vitamin A value, equivalent to 1.5 LBU is lower than that in the normal group, or that found in the colitis group, the range is less, the low value is below in either of the other groups, and the standard deviation is lower. The average carotene value, however, 0.87 LYU is higher and the range is greater. The lowest value is below that in the control group and is equal to that in the colitis group. The average Vitamin C level, however, of 0.51 mgs. per 100 cc. is lower than in either group and lies at the scorbutic borderline. There is little difference in comparison of ranges. The standard deviation, however, is lower.

One hundred and twenty-one miscellaneous ward patients have been studied in similar fashion as a second control and are presented without respect to diagnosis and without reference to duration of hospital residence. (Graph 4). Vitamin A determinations have been made on one hundred and fourteen. The average, equivalent to 1.5 LBU, corresponds to the

TABLE IV
Miscellaneous ward patients

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	116	121	108
Ave. Finding	1.5 Blue units	0.87 Yellow units	0.64 mg. %
Range	3.5 — 0.6	3.2 — 0.2	2.90 — 0.10
St. Deviation	0.19	0.53	0.45
St. Deviation Means	0.02	0.05	0.05
Probable Error	0.01	0.03	0.03

finding in the ulcer cases and is below the level of the normal and the colitis groups. The range is greater than in the other three groups. The lowest value is lower, and the standard deviation is less.

The carotene level, 0.87 LYU, is comparable to those in the ulcer and colitis groups, and is above the level observed in the normal controls. The range and the

standard deviation are greater than in any of the three groups. The average Vitamin C level, 0.64 mgs. per 100 cc. is intermediate between those of the ulcer and the colitis cases. The range, however, is greater than that in any of the other groups.

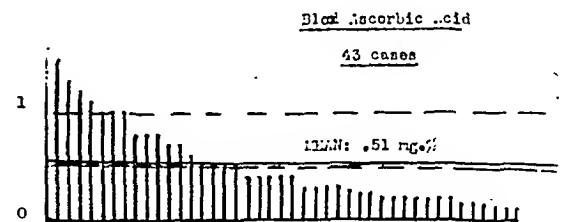
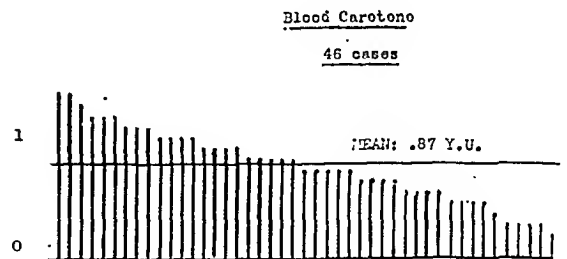
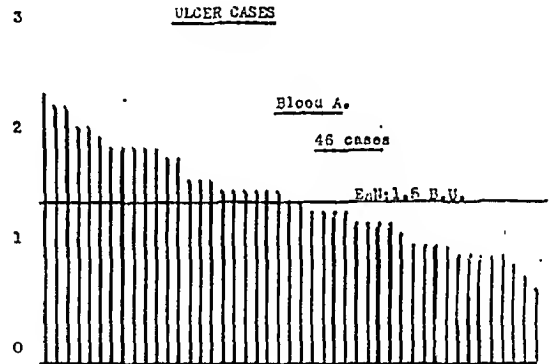
VITAMIN K

Prothrombin determinations have been made on sixty-nine miscellaneous cases. Three individuals have shown a definite elevation of prothrombin time. It is of interest to note that jaundice was not present.

DISCUSSION

The methods used for estimation of blood Vitamin A and carotene are admittedly inexact as in any colorimetric procedure which is based upon a transitory end point. This potential source of error is probably magnified to some extent when readings are made by eye rather than by photoelectric equipment. With practice, however, satisfactory uniformity of results can be obtained on duplicate specimens. Since there is an inherent and unavoidable error in the method it

SCALE



Graph 3

has seemed best not to magnify this error by the effort to translate blue units into U.S.P. units of Vitamin A, and yellow units into milligrams of carotene. Since exact human standards are either unknown or still subject to discussion it was decided to use the values observed in our normal group as the standard for comparison. A chart has been constructed on which are plotted as zones the "A," carotene, and "C" values obtained from the normal group. Each of these zones

therefore is not an accurate index of saturation or depletion. Similarly the plasma carotene appears to be a measure of the difference between rate of absorption and rate of conversion to Vitamin A rather than an index of reserve or intake.

The normal range for blood Vitamin C is well established.

We have no basis for contrasting the Vitamin A values in our normal controls with other findings reported in the literature. The blood carotene average is definitely below the level reported by Clausen (3) for normal children. Our control group as a whole appears somewhat deficient in Vitamin C. Ten had 0.5 mgs. per 100 cc. or less. Only twelve reached or exceeded 1.0 mgs. per 100 cc.

The average values observed in the cases of chronic ulcerative colitis probably do not present a true picture. Many of these individuals had been under observation for considerable periods in the Outpatient Department where they had received careful dietetic instruction from a trained dietitian. Moreover in most instances they were receiving supplemental vitamin medication. It is significant, however, that the lowest values for "A" and "C" were below the lowest values observed in the control group.

The findings in the ulcer cases, on the other hand, are not weighted by previously given vitamin medication or carefully supervised diets. The observations in this group were made on consecutive ward admissions within twenty-four to forty-eight hours after entry into hospital. The average values for Vitamin A and Vitamin C are distinctly lower than those in the control group, and the minimal values likewise are lower. Our Vitamin C findings confirm the previously reported results of Portnoy and Wilkinson (15) and Lazarus (16).

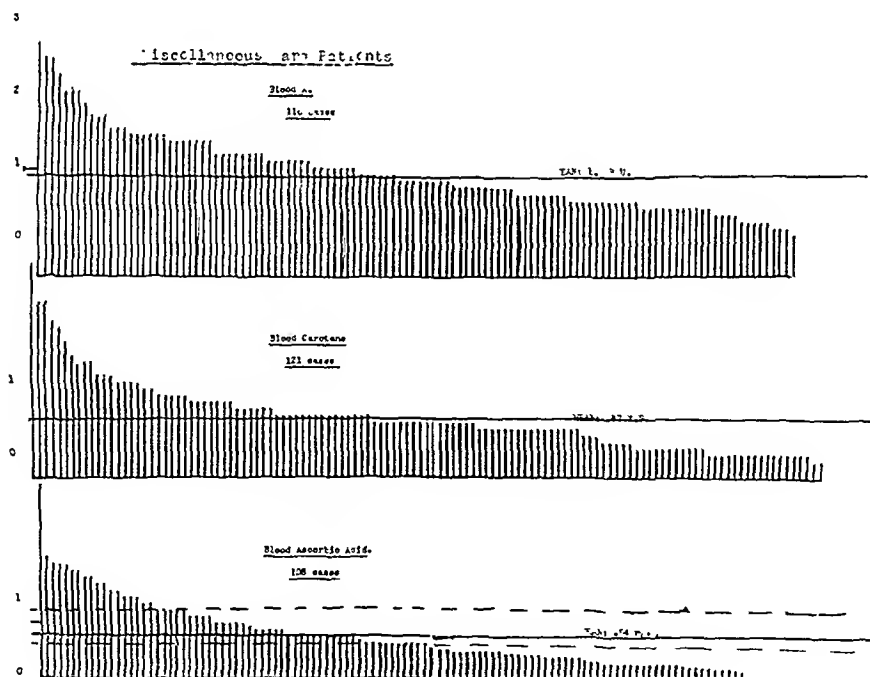
The data obtained from the miscellaneous group do

Vitamin K

No. cases tested	Prothrombin Time	Diagnosis
69		
Elevated Prothrombin time		
1. S.B.	3 min. 12 sec	Ulcerative Colitis
2. M.A.	6 min —no clot	Chronic Enteritis
3. E.F.	1 min 3 sec.	Sprue

is derived by applying the standard deviation to the average.

The resulting "normal" chart (Graph 5) however is undoubtedly normal in a relative sense only. Present information does not permit definition of the normal level of blood Vitamin A or carotene. Since several of our control group revealed Vitamin C levels below the scorbutic threshold it is improbable that the lowest values for Vitamin A and carotene represent optimal values. Furthermore, requirements undoubtedly vary under differing physiologic and pathologic conditions. Moreover, Bessey and Wolbach (14) have pointed out that the concentration of Vitamin A in the blood is independent of the amount stored in the liver and



Graph 4

not permit of any definite conclusions. In general the values fall between the ulcer cases on the one hand and the colitis and normal groups on the other. This finding is to be expected in individuals either chronically or acutely sick who have not been receiving supplemental vitamin medication. One striking finding, however, in this group, the frequency of low Vitamin C levels, is well shown on Graph 4. This may be explained by poor diets prior to entry, increased metabolic demands, or hospital diet which is inadequate to meet the apparent high requirements of these patients.

It is of interest to note that the carotene values in the colitis, the ulcer, and the miscellaneous groups, are definitely above the average of the normal groups. The significance of this is not clear.

Despite the sources of error at present inherent in blood Vitamin A determinations, the findings in our

The past history is irrelevant except for chronic sinusitis, bleeding gums at times and cutaneous ecchymoses following slight trauma.

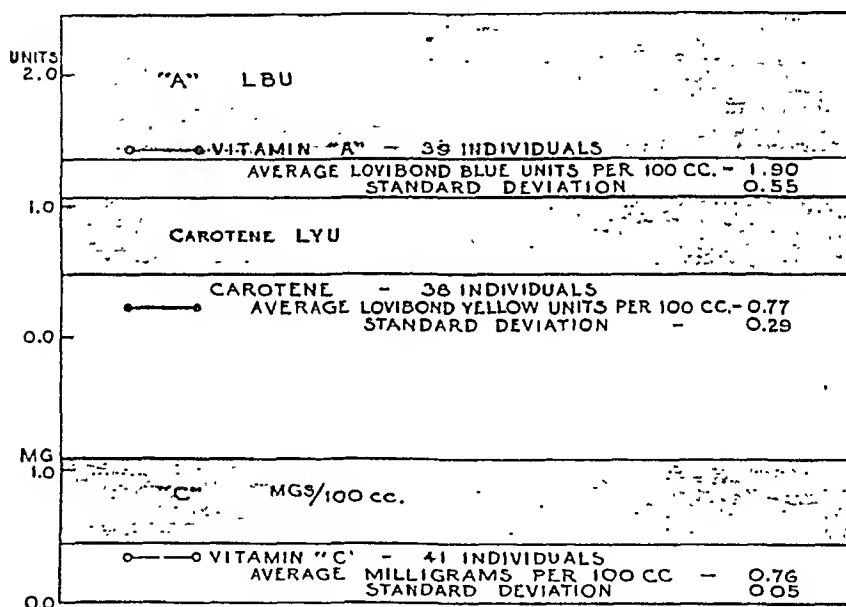
Physical examination revealed a poorly nourished pale, chronically sick young woman. The tongue was normal and the teeth and gums in good condition. No abnormalities of the skin were noted. The heart and lungs and abdomen were negative. Proctoscopic examination revealed a swollen acutely inflamed mucosa oozing blood freely.

She was followed in the Outpatient Department for two weeks and then admitted on January 11th because of increasing weakness, persistent diarrhea and profuse rectal bleeding. On two occasions just prior to hospitalization she vomited small amounts of blood.

TREATMENT

At the first visit to the Outpatient Department she was referred to the dietitian and instructed to take a diet containing adequate sources of Vitamin C. During the second week Vitamin A, 26,600 units, in the form of oleum per-

FASTING BLOOD VITAMIN VALUES - NORMAL INDIVIDUALS



Graph 5

hands parallel the clinical condition in many patients. Low values have been amply confirmed by correlation with well recognized physical signs. The value of repeated Vitamin A, C and occasionally K estimations is illustrated by the following cases.

CASE ABSTRACTS

R. P.: Age 30. The patient is a thirty year old Italian American housewife who was first seen on December 28, 1938. Four years previously she developed a gradually increasing diarrhea with bleeding from the colon. This attack subsided in the course of a month and was followed by a year of freedom from symptoms in which she gained 18 pounds. The second attack followed oophorectomy and appendectomy. A third episode occurred 2 years later and again cleared up in a reasonable period of time. The fourth attack began five weeks prior to admission with gradually increasing diarrhea with mucus and blood in the stools. Since the onset of this last attack she had been on a restricted soft diet with boiled meats but had had no fruit juices, fruits or vegetables.

comorphum were given daily. From January 11th to January 19th treatment was by diet alone. On the latter date Vitamin A 13,300 units daily in the form of oleum percomorphum was added and continued throughout the period of observation. No other supplemental sources of Vitamins A or C or carotene were given. (Graph 6).

VITAMIN ASSAYS

On December 29th the fasting blood values were as follows: Vitamin C 0.2 mgs. per 100 cc.; Vitamin A 1.1 Lovibond blue unit equivalents; Carotene 0.6 Lovibond yellow unit equivalents. On January 11th and 12th the Vitamin C level had risen to 1.1 mgs. per 100 cc. Thereafter it remained at normal or saturation levels. The prothrombin time on January 11th was found to be 47 seconds falling to normal on January 17th.

The blood Vitamin A remained at the low level of 1.1 LBU per 100 cc. through January 19th. Daily administration of 13,300 units of "A" thereafter was followed by progressive rise to the normal zone.

The blood carotene curve irregularly parallels the Vitamin "A" curve.

COMMENT

This patient's diet was grossly deficient in sources of Vitamins C and K and probably lacking as well in thiamin, A and D. On dietary management alone the blood Vitamin "C" returned to normal levels within two weeks. The prothrombin time likewise fell to normal. Cessation of rectal bleeding coincided roughly with the restoration of these values to normal. Daily administration of 13,300 units of Vitamin A in the form of oleum percomorphum was accompanied by a progressive rise of the blood "A" values toward normal levels.

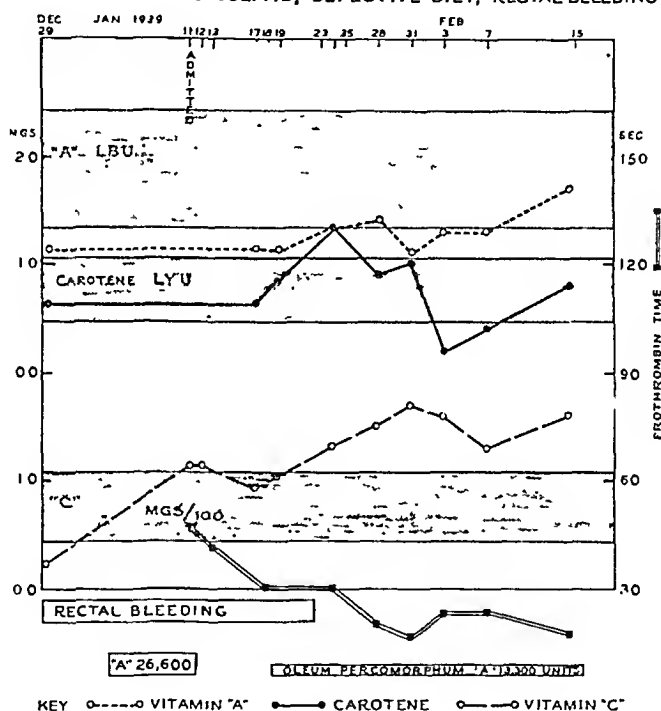
This patient therefore exhibited a multiple deficiency involving at least Vitamins A and C. The slightly but definitely elevated prothrombin time noted after two weeks on a properly balanced diet, and the relatively close association in time between cessation of rectal bleeding

out fever and without evidence of organic cardiac disease. The ankle jerks were not obtainable. Proctoscopy revealed an advanced but relatively quiescent ulcerative colitis without evidence of bleeding. Barium enema showed total involvement of the colon. X-ray examination of the skeleton is reported as follows: "Skeletal epiphyses were examined and the development is in keeping with that of a twelve year individual." (Graph 7).

VITAMIN ASSAY

Vitamin assay on admission revealed a normal blood carotene and Vitamin "C," and a very low Vitamin A. The values were 0.9 LYU, 1.1 mgs. per 100 cc. and 1.0 LBU respectively. The prothrombin time 49 seconds, was slightly elevated. In view of these findings the base diet was supplemented by Vitamin A 26,600 units per day in the form of oleum percomorphum. This was followed by a definite rise in the blood A curve which however levelled

R P AGE 30 ULCERATIVE COLITIS, DEFECTIVE DIET, RECTAL BLEEDING



and normal prothrombin levels suggest a Vitamin K deficiency as well. Improvement in the blood vitamin levels was accompanied by definite general clinical improvement.

R. W.: The patient is a seventeen year old American boy who was admitted to the hospital on January 15, 1939. Five years previously he developed what was diagnosed as chronic ulcerative colitis following an attack of typhoid fever. There were repeated recurrences. During the ten months prior to admission he had had persistent diarrhea without gross blood in the stools. During the past two years he lost thirty pounds in weight.

Physical examination revealed a greatly emaciated underdeveloped boy. Stature was much below normal. The genitalia were undeveloped and there was no axillary or pubic hair. The tongue was definitely smooth but not red or inflamed. The skin was exceedingly dry, harsh, and scaly, and the mucous membranes pale. Two chronic ulcers of four months duration were present in the skin of the abdomen. There was a marked tachycardia with-

off at 1.5 LBU. Because of this the oleum percomorphum by mouth was supplemented by daily injections of 15 cc. of cod liver oil. This combined therapy was given from January 31st to February 7th inclusive when both were discontinued. On the latter date the blood A had reached 1.7 LBU and despite ileostomy the following day the "A" values rose to 2.1 LBU on the 13th. Three days later it had fallen 1.3 LBU, at which time oral administration was resumed.

The blood carotene curve varied irregularly throughout the period of observation.

The blood Vitamin "C" fell slowly following admission to 0.6 mgs. per cent. At this time 1.0 gms. of cevitamic acid by mouth was given daily through February 7th. The curve promptly rose to the normal range, falling again in the post-operative period to 0.3 mgs. per 100 cc.

The prothrombin time fell to normal without supplemental medication.

The patient was discharged on March 23rd much improved, having gained twelve pounds.

COMMENT

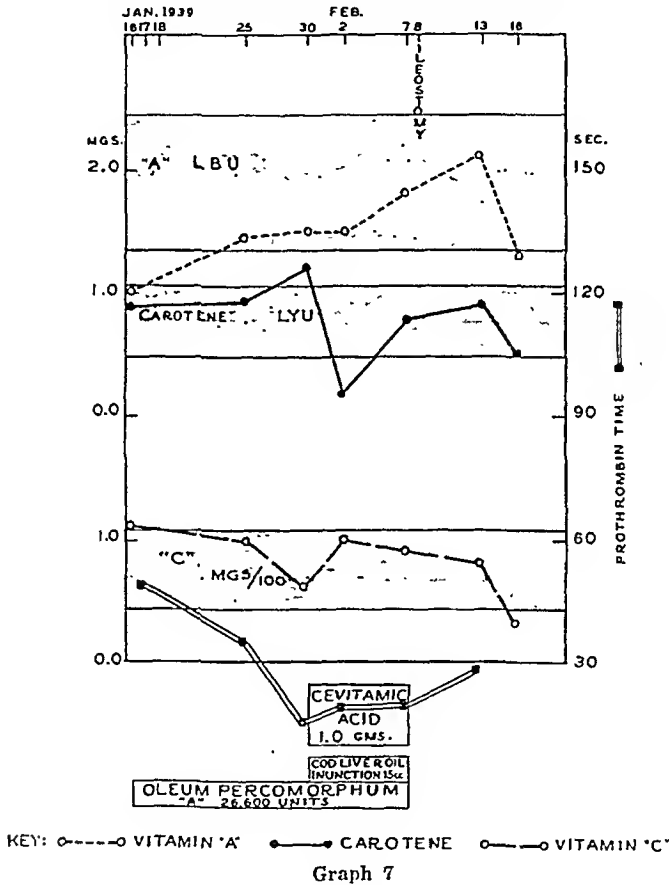
This patient on admission presented clinical evidence of advanced deficiency disease characterized by arrested growth, emaciation, anemia, delayed puberty, arrest of bone development and the skin changes associated with Vitamin A deficiency. The bone changes demonstrated by X-ray are characteristic of recurrent rickets and also of experimental "A" deficiency in animals. Treatment was guided by the vitamin assays and the date of operation based upon the observed curves. The unusually smooth convalescence we attribute in no small part to the correction of the observed deficiencies.

examination revealed an acute diffuse inflammatory process throughout the visualized area with moderate bleeding. Barium enema showed involvement of the entire colon. There was a moderately severe anemia. Macrocytes and nucleated red cells were seen in the stained blood film.

COURSE

During the ensuing weeks he developed a variety of complications. The tongue and buccal mucosa became red, inflamed and painful, presenting the characteristic appearances of acute pellagra. Parenteral liver extract (Lilly 343) failed to control the oral condition until 600 mgs. of nicotinic acid daily was added. Two perirectal abscesses required surgical drainage. The general condition became increasingly unsatisfactory, with progres-

R.W. AGE 17: ULCERATIVE COLITIS, GROWTH FAILURE, DELAYED PUBERTY, MALNUTRITION



S. B.: The patient was a twenty-one year old American male who was admitted to the hospital on September 13, 1938. Six weeks previously he developed a gradually increasing watery diarrhea, weakness and progressive loss of weight.

The past history was non-revealing.

On admission he showed marked emaciation and pallor. The tongue was smooth but not inflamed and there were scattered aphthous ulcers on the buccal mucosa. The skin was very dry and slightly hyperkeratotic. Heart and lungs were negative. There was tenderness over the colon and a palpable dilated cecum. Hyperesthesia and paresthesia were noted over the dorsum of the right foot. The right patellar reflex was less active than the left. Proctoscopic

sive weight loss, septic temperature curve, and evidence of renal irritation. By mid-December surgery seemed to offer the only hope of survival. Recognizing the seriousness of the risk ileostomy was performed on December 10th. Six days later he developed what appeared to be acute sepsis. The ileostomy drainage consisted of tarry material giving a strongly positive benzedine reaction, there was blood in the urine, the entire body was studded with cutaneous petechiae, and there was a massive subcutaneous hemorrhage in the left leg. There was no reduction of blood platelets. The appearance of these signs was accompanied by shock which was controlled by transfusion. Death occurred nine days later from inanition without evidence of further hemorrhage. (Graph 8).

VITAMIN ASSAYS

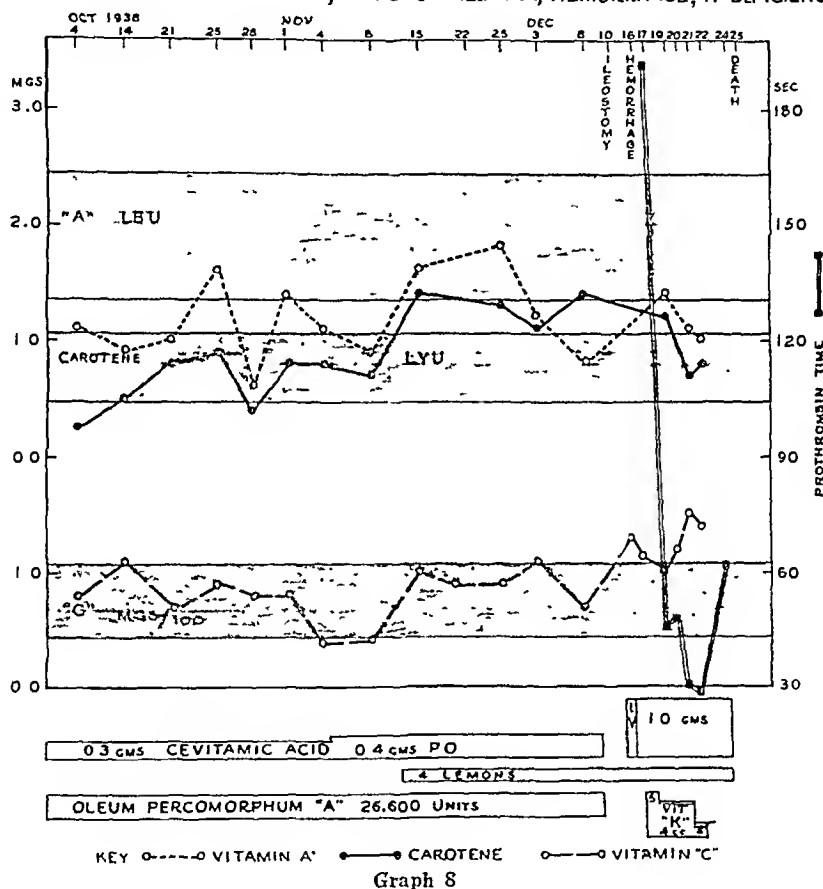
It was impossible to do a blood vitamin assay until two weeks after admission. Because of the obvious malnutrition and the rectal bleeding he was placed at once on 300 mgs. cevitic acid by mouth daily and 26,600 units of Vitamin "A" in the form of oleum percomorphum. On October 4th the blood Vitamin A and carotene were both at low levels, 1.1 LBU and 0.25 LYU respectively. The Vitamin C content was 0.8 mgs. per 100 cc. During the period of observation the Vitamin A curve fluctuated irregularly seldom reaching normal values. The initial dosage of oleum percomorphum was continued unchanged. The blood carotene curve showed a sustained rise until operation on December 10th when it dropped again moderately. The Vitamin C content remained at normal levels

when it was found to be 1.3 mgs. per 100 cc. The following day the prothrombin time was found to be 192 seconds. Through the courtesy of E. R. Squibb & Co. we were able to obtain a Vitamin "K" concentrate containing 500 units per cc. Five cc. were given by mouth on December 18th and four cc. 19th, 20th and 21st and two cc. on the 22nd. The prothrombin time was thirty-one seconds on the 21st and twenty-nine seconds on the 22nd. On December 21st, two days after discontinuing the "K" concentrate, the prothrombin time had again risen to 62 seconds. Bile salts were not administered.

COMMENT

This patient presented a severe mixed deficiency state characterized clinically by pseudo-pellagra, macrocytic

S.B. AGE 21 · ULCERATIVE COLITIS, PSEUDO-PELLAGRA, HEMORRHAGE, "K" DEFICIENCY



until November 4th when it had fallen to 0.4 mgs. per 100 cc. The daily dosage of cevitic acid was then increased to 400 mgs. This was followed by a rise of the curve into the normal range. On December 8th, 2 days prior to operation, the blood "C" was 0.7 mgs. per 100 cc. For a month before this date the diet had been supplemented by the juice of four lemons daily. All medications were stopped the day of operation. Fluids by mouth including fruit juices were resumed the day of operation and soft diet on the 13th.

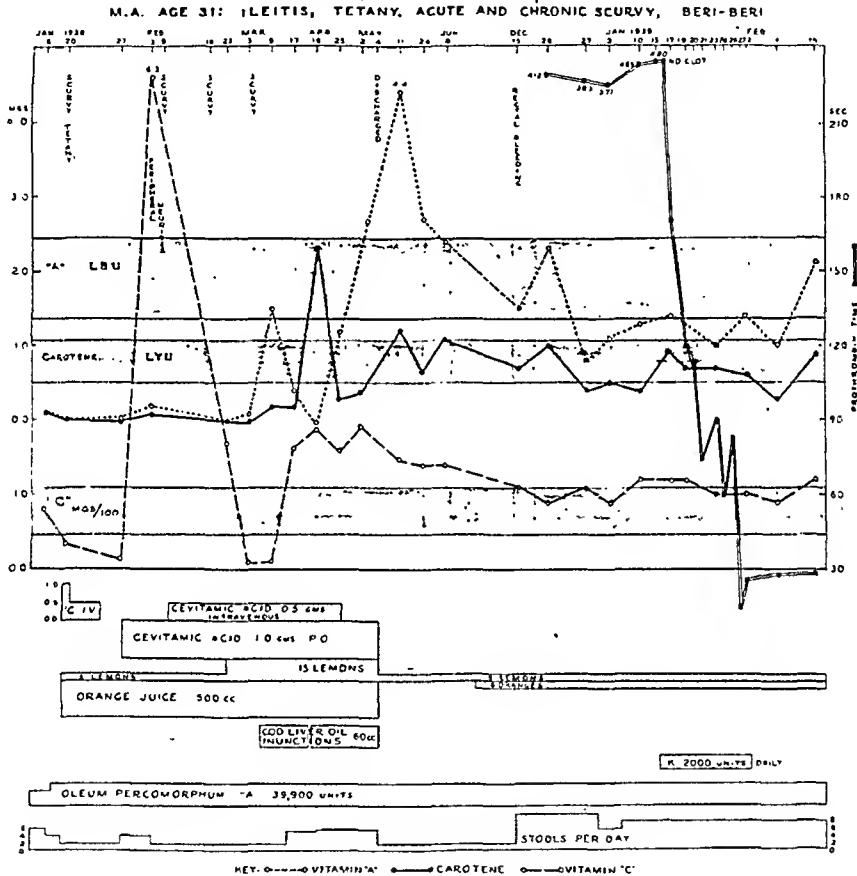
With the onset of the acute hemorrhagic episode the patient was given a transfusion of 750 cc. of citrated blood, and 1.0 gms. of cevitic acid intravenously. Because of the gravity of his condition a blood Vitamin C determination could not be made until some hours later

anemia, and an acute hemorrhagic episode presenting the clinical phenomena of scurvy. Unfortunately it was not deemed wise to take blood for vitamin assay during the immediate post-operative period. The blood Vitamin "C" curve throughout the period of observation and the resumption of fruit juices within twelve hours of the operative procedure led us to believe that there was no danger of deficiency of this factor. It is unfortunate that a "C" determination could not be done prior to the transfusion and the intravenous administration of cevitic acid. The observed value of 1.3 mgs. some hours later, however, does not suggest the existence of a "C" deficiency sufficiently severe to explain the clinical picture. It was of great interest to find the marked "K" deficiency in the absence of jaundice and likewise to observe the return of pro-

thrombin time to normal levels after the administration of 13 cc. of concentrate containing a total of 6,500 units of Vitamin "K." This was effective without the administration of bile salts. Although the cause of the hemorrhages cannot be stated positively in this instance, it seems probable that the "K" deficiency alone or in combination with a moderate deficit of "C" were responsible.

M. A.: The patient is a thirty year old Jewish male who was first seen on September 1, 1932. He gave a history of recurring attacks of chronic ulcerative colitis for three and a half years with recent recurrences. The history was irrelevant otherwise. Physical examination revealed nothing of note apart from proctoscopy which showed an acutely inflamed mucosa. Barium enema demonstrated a normal colon proximal to the sigmoid. Small in-

were no clinical indications of deficiency disease. Shortly thereafter small intestine X-rays revealed the characteristic changes seen in deficiency disease and suggestive evidence of new areas of regional enteritis. He was readmitted to hospital. In mid-December subacute glossitis appeared. There was a mild hypochromic anemia. The laboratory findings were suggestive of sprue. Consequently he was placed on a high protein low fat diet supplemented by large dosage of Vitamins A and D, and a rich source of B complex. There was no improvement on this regime and heavy parenteral dosage of liver extract had no apparent effect other than to correct the glossitis. Stools averaged from six to ten daily and from December 24th were controlled by opium and opium derivatives.



Graph 9

testine X-rays, however, suggested an organic lesion of the terminal ileum.

The colitis was brought under prompt control by dietary management and vaccine. There has been no recurrence.

In 1935 he began to have mild symptoms of intestinal obstruction and diarrhea. This condition became chronic. By February of 1937 the symptoms had developed to a point requiring hospitalization. A month later ileo-transverse colostomy was performed and subsequently resection of the diseased portion of the ileum and the proximal colon. The anatomic diagnosis was chronic non-specific enteritis. Convalescence was smooth.

In October of 1937 he returned complaining of increasing flatulence, distention and loose stools. The feces resembled those of sprue. The tongue was normal and there

On January 16th he complained of severe pain in the right gluteal region at the site of a previous liver extract injection. Examination revealed a large area of induration, increased heat, and extreme tenderness. Urinalysis at this time was negative.

The following day his condition was exceedingly grave. He was coughing and spitting considerable amounts of blood. There were large subcutaneous hemorrhages in the right upper arm. There was continuous oozing from a venipuncture in the ante-cubital fossa. The feces were tarry and contained bright blood. There was emesis of coffee ground material. He was unable to void and catheterization yielded grossly bloody urine. The hemoglobin had fallen to 32% (Sahli) and the erythrocyte count to 1,600,000. He complained of muscle cramps during the

morning and in the afternoon he developed a series of attacks of typical acute tetany. This acute episode was controlled by transfusion of 600 cc. of citrated blood, and by intravenous administration of 1.0 gm. of cevitic acid and 60 cc. of 10% calcium gluconate solution.

For the next five days 0.5 gms. of cevitic acid was given daily by vein. The fruit juices of the diet were permanently supplemented by 500 cc. of fresh orange juice and the juice of five lemons each day. By January 27th gross bleeding had ceased. The blood Vitamin C, however, was low and consequently 1.0 gm. of cevitic acid by mouth daily was added and given continuously thereafter.

During the latter part of January the patient complained bitterly of increasing pain in all four extremities and of paresthesias of the hands and feet. By February 5th a frank peripheral neuritis of both arms and legs was evident, with marked motor weakness, muscle tenderness and diminished or absent deep reflexes. It was apparent that the clinical picture was further complicated by a classical beriberi. Consequently he was put on daily parenteral dosage of 3000 international units of thiamin.

February 6th cutaneous ecchymoses again appeared. Daily intravenous administration of 0.5 gms. of cevitic acid was added. Two days later there was bleeding from the mouth and gums, ecchymoses and petechiae were scattered profusely over the entire body, and another attack of hematemeses occurred. Every hypodermic puncture was surrounded by an ecchymotic areola and slow continuous oozing of blood occurred from some. The hemoglobin was 44% (Sahli) and the erythrocyte count 1,900,000. A series of large transfusions were given.

On February 19th hemorrhagic areas reappeared in the buccal mucosa. A venipuncture oozed continuously for forty-eight hours. Four days later there was profuse bleeding from the gums and a newly-developed ulcer at the tip of the tongue. There were multiple subcutaneous hemorrhages and a large deep hemorrhage in the tissues of the left upper arm. The following day the Vitamin C sources were supplemented by the addition of the juice of ten lemons. This was continued up to the time of discharge. Slight bleeding from the gums continued intermittently. New bleeding areas developed on the base of the tongue, the floor of the mouth and the frenum.

During the first week in March he complained of pain in the left side of the neck. This was accompanied by swelling, induration and marked tenderness. Simultaneously a large submucosal hemorrhage appeared on the left side of the uvula and wall of the pharynx producing some respiratory obstruction and marked difficulty of deglutition. Bleeding ceased after March 7 and the patient made a slow but satisfactory convalescence. He was discharged on May 4th and has been followed at weekly or two weekly intervals in the Outpatient Department.

His subsequent course was uneventful until mid-December of 1938 when he began to pass considerable amounts of blood by rectum. Anoscopic, proctoscopic and X-ray examinations failed to reveal the source of bleeding. Repeated prothrombin determinations revealed no clot formation. There was no jaundice. Exhibition of Vitamin K 2000 units daily, kindly supplied by E. R. Squibb & Co., rapidly restored the prothrombin time to normal and diminished but did not entirely stop the bleeding. Bile salts were not administered with the "K" concentrate. (Graph 9).

VITAMIN ASSAYS

The first vitamin assay was done on January 6, 1938. The values for "A" and carotene were extremely low 0.1 LBU and 0.1 LYU respectively. The Vitamin C content 0.8 mgs. per 100 cc. was within the normal range. On January 20th, 3 days after the onset of acute scurvy and after 2.0 gms. of cevitic acid intravenously in the preceding three days the Vitamin C level had fallen to 0.3 mgs. per 100 cc. and on the 27th to 0.14 mgs. per 100 cc.

despite the addition of 500 cc. of fresh orange juice and the juice of four lemons each day. The further addition of 1.0 gm. of cevitic acid by mouth each day was followed by a rise to 6.3 mgs. per 100 cc. on February 3rd. On the 6th because of renewed bleeding half a gram of cevitic acid each day intravenously was added to the schedule already in force. Withdrawal of blood for vitamin assay was not deemed advisable until February 23rd when the "C" content was 1.72 mgs. per 100 cc.

On the 24th the "C" sources were still further increased by the juice of ten additional lemons each day. On March 3rd and March 8th the blood "C" level remained at 0.1 mg. per 100 cc. coinciding with the final acute hemorrhagic episode. Throughout the remainder of the period of observation the blood "C" content remained within the normal range. Following discharge from the hospital the diet was supplemented by the juice of five lemons daily, and for most of the time by six oranges each day as well.

The blood Vitamin A level ranged from a trace to .2 LBU from January 6th through March 3rd despite the daily oral administration of 39,900 U.S.P. units of Vitamin A in the form of oleum percomorphum. From March 7th to May 4th with the exception of one day 60 cc. of cod liver oil were given daily by injection. There was an immediate rise and equally abrupt fall of the "A" curve followed by a sustained rise to 4.4 LBU on May 11th, a week following discharge from the hospital. Thereafter despite the continued oral administration of 39,900 units of Vitamin "A" in the form of oleum percomorphum the curve followed an irregular downward trend never, however, reaching the previous low levels.

The curve of blood carotene irregularly paralleled the Vitamin "A" curve.

The occurrence of rectal bleeding in December was not associated with an abnormal blood Vitamin "C" curve. Prothrombin determinations on six successive occasions showed complete failure of clot formation, the last on January 16, 1939. Vitamin "K" concentrate kindly supplied by E. R. Squibb & Co. was started on this date in daily dosage of 2000 units and continued through February 3rd. The prothrombin time dropped abruptly reaching 15 seconds on January 27th. There was no jaundice. The icterus index was normal. Bile salts were not administered with the "K" concentrate.

This patient must be regarded as a case of conditioned deficiency disease secondary to regional enteritis, presenting the characteristics of acute and chronic scurvy, acute tetany, acute beriberi, and nine months later acute Vitamin "K" deficiency in the absence of jaundice, with normal icterus index, and without other signs of hepatic disease.

SUMMARY

Accurate methods are now available for blood Vitamin C and K determinations. Although the technique and interpretation of Vitamin A estimations are open to criticism they are sufficiently accurate to have clinical value. Studies of a group of apparently healthy normal adults have been utilized to plot zones of apparent normality for Vitamins A, carotene, and C. Although the low limits found in the normal group cannot be accepted as the low limits of physiologic requirements, they constitute a useful basis for comparison. Our findings indicate that a significant proportion of healthy individuals taking average diets are well below the optimal level of blood Vitamin C. It is probable that certain of the A values are likewise low. The average Vitamin A and C values in a consecutive series of peptic ulcer cases are below the averages of the normal group, and the Vitamin C level is frequently very low. Similar deficiencies are not infre-

quent in chronic ulcerative colitis, and in the general ward population.

Repeated vitamin determinations have proved to be of inestimable value in the management of individual patients. They permit intelligent and controlled therapy of deficiency states. It is of interest that inunction of cod liver oil has proven to be an effective method of raising the blood Vitamin A level. It is likewise of interest to note that in certain severe deficiency states uncomplicated by jaundice a marked defect in prothrombin may occur associated with hemorrhage and responding promptly to the administration of Vitamin K concentrate without bile salts.

CONCLUSIONS

1. Subclinical vitamin deficiency states are not uncommon.
2. Methods of vitamin assay and normal standards are sufficiently accurate for clinical purposes.
3. Repeated vitamin assays frequently provide a most important guide to therapy.

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DISCUSSION

DR. HEINRICH NECHELES (Chicago): In view of the previous two papers, I should like to point out the importance of the factor of absorption in the gastro-intestinal tract, which seems to be overlooked by a number of investigators. If vitamins are given by mouth and cannot be absorbed, it is as good as if they are not given. We have seen that in patients and animals, and I very much feel that the ultimate way out will be to have most vitamins in soluble preparations for injections.

In all cases of atrophy or inflammation of the gastro-intestinal mucosa, or of diarrhea, administration by mouth, even of huge doses, may be useless.

Another point I want to make is that although it is believed that single, isolated vitamins are specific for certain clinical conditions, it becomes more and more evident that we have to administer groups of vitamins, and that seems to be quite evident from previous papers. For instance, the conviction is growing in many observers that in pellagra, it is not nicotinic acid alone, which ultimately cures, but a combination of several factors of the B group.

To give yeast is pretty useless in a number of patients because yeast is hydrolyzed with difficulty. In the absence of essential ferments, especially of trypsin, the yeast is utilized little or not at all, and it would be very good if yeast would be eliminated entirely from cases that have a disturbance in their digestive canal and an injectible yeast extract used instead.

Clinical Observations on the Possible Relationship of Digestive Tract Disease to a Type of Osteoporosis*

By

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and

ROBERT PAUL MEADER, M.D.

WITH the advancement in knowledge of nutritional and endocrine disorders and development in roentgenologic and chemical methods more attention has been called to disorders of mineral metabolism. Generalized demineralization of bone is observed to a striking degree in hyperparathyroidism, further characterized by a high serum calcium and low serum phosphorus. Numerous reports in the literature (1, 2, 3) mention association of osteoporosis in some instances of long standing hyperthyroidism, the exact mechanism by which this occurs being rather uncertain or obscure, but indicative of the more extensive alteration of the metabolic physiology in this disease. Generalized demineralization of bone has been

observed in cases of long standing nephritis (4, 5) referred to as hyperparathyroidism secondary to renal functional impairment, and related to the retention of phosphates because of the inability of the kidney to excrete them adequately. Chronic steatorrhea may be accompanied by osteoporosis, probably due to excessive loss of calcium in the feces (6, 7). Poorly balanced or deficient nutrition may be important in the production of osteoporosis. A recent editorial in the Journal of the American Medical Association on senile osteoporosis (8) relates that the "theory that protracted deficiencies in basic nutrition resulting from poor dietary habits may impair the health of the adult and contribute to the factors which produce disabilities commonly attributed to 'old age' has rarely been postulated," and calls attention accordingly that "gradual demineralization of the skeleton over a

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period of years may result in pathologic changes in the kidneys or other vital organs and hence affect unfavorably the health of the patient." Furthermore, it is stated that "generalized osteoporosis in the adult can be explained only on a basis of chronic or intermittent negative mineral balance over a period of many years."

Demineralization of the skeleton represents an important degree of depletion of storage of calcium and indicates an inadequate absorption or an increased excretion of calcium over a long period. Apparently the physiologic process is able to maintain a surprisingly constant level of the transport calcium, and for this reason cases of osteoporosis may be free from symptoms due to hypocalcemia or hypercalcemia. Calcium absorption may be increased (9) by a high calcium diet, cod liver oil (Vitamin D), increased intestinal acidity by converting insoluble phosphate into soluble compounds of calcium, and systemic acidosis; and calcium absorption may be decreased by diarrhea, a low calcium diet, a high phosphorus diet, poor utilization of fat and fatty acid, and alkalinity of the intestinal contents.

TABLE I

Age	G. I. Symptoms		No G I Symptoms		Total
	Male	Female	Male	Female	
Under 30	0	0	1	0	1
30-39	0	1	0	1	2
40-49	0	3	0	0	3
50-59	1	6	0	5	12
60-69	1	6	2	16	10
70-79	2	2	2	6	12
80 or over	0	0	0	1	1
Sub-total	4	18	5	23	50
Total	22		28		50

In support of the view that absorption of calcium is decreased by insufficient acid reaction of the contents of the upper small intestine, Bussabarger, Freeman and Ivy produced severe homogeneous osteoporosis by gastrectomy in puppies (10). Osteoporosis might be expected in achlorhydria of long standing.

Occasional severe generalized osteoporosis is encountered in the adult in an age before senility, and unaccompanied by the change in blood chemistry characteristic of hyperparathyroidism. Such patients often complain of generalized aches and pains and weakness and not infrequently have vague gastro-intestinal symptoms. As the age of 60 is approached it is often difficult to separate such cases from so-called senile osteoporosis, but it can be said that such osteoporosis may exist without other characteristics of senility.

Fifty cases of generalized osteoporosis were selected for study. None of these cases had the characteristic changes in blood chemistry of hyperparathyroidism. Undoubtedly some of the cases of older age were cases of senile osteoporosis, but there was a sufficient number under the age of 60 without other evidences

of senility to be significant for the purposes of this study. All of these cases had a sufficient degree of osteoporosis to be easily recognized from the roentgenograms. A standard technique in taking films and extreme caution is necessary to avoid error in interpretation of the presence or absence of osteoporosis. It has been estimated that in decalcification the calcium loss must be from 20% to 40% in order to be

TABLE II

Gastro-intestinal symptoms in twenty-two cases of osteoporosis

Symptom	No. of Cases
Anorexia	9
Nausea	10
Vomiting	7
Vague abdominal pain	8
Diarrhea	1
Constipation	16
Indigestion, Vague, unqualified	9
Sensation of fullness in abdomen	8

visible by X-ray (11). Therefore, these cases represent severe osteoporosis. The difficulty in recognizing lesser degrees of osteoporosis may account for the many diagnoses of neurosis or other functional disturbance so long before the true mineral metabolic disorder is discovered.

Of these 50 patients 22 or 44% had gastro-intestinal symptoms. Since we are interested here particularly in those with gastro-intestinal symptoms the other 28 are not included in this report other than to correlate their age and sex incidence which is demonstrated in Table I.

Of the cases with gastro-intestinal systems 18 or 82% were female and 4 or 18% were male. The ages range from 34 years to 71 years; eleven or 50% were under 60 years of age, and in this group there were 10 females and 1 male. In the group over 60 years of age there were 8 females and 3 males. The sex and age incidence was fairly comparable to that of the group in which there were no gastro-intestinal symptoms.

TABLE III

Duration of G. I. symptoms range from 1 month to 20 years

1 year or under	9
1-5 years	3
5-10 years	5
10-20 years	5
Total	22

The gastro-intestinal symptoms in order of their frequency were: constipation; nausea; vague, unqualified indigestion; anorexia; vague abdominal pains; sensation of fullness in the abdomen, and occasional vomiting.

In the cases of long duration the symptoms were variable but some time during the history several of these symptoms were present alone or in combination.

The gastro-intestinal symptoms ranged in duration 1 month to 20 years, the majority having symptoms over 1 year and nearly one-half of the cases had symptoms over 5 years.

Organic digestive tract disease was demonstrated in 11 or 50% of the cases and for this reason it is difficult to evaluate the origin or significance of the gastro-intestinal symptoms. The diagnoses of the organic conditions are listed in Table IV.

TABLE IV

Organic digestive tract disease in 22 cases of osteoporosis having gastro-intestinal symptoms

Chronic Cholecystitis without stones.....	3
Chronic Cholecystitis with stones	1
Duodenal ulcer	1
Chronic esophageal ulcer	1
Carcinoma colon	1
Carcinoma rectum	1
Diabetes mellitus	3
Total	11

The four cases of gall bladder disease were proven at operation. The duodenal ulcer was proven by X-ray and was accompanied by a typical hyperacidity curve. The esophageal ulcer was demonstrated by X-ray and esophagoscope, and malignancy has been ruled out by healing with stricture and long duration of life. The two cases of carcinoma of the lower bowel had symptoms referable to the local lesions only a short time and it seems reasonable that other very chronic gastro-intestinal symptoms were on some other basis. It is doubtful whether any gastro-intestinal symptoms should be attributed to the diabetes in the three cases included.

Further analytical breaking up of the remaining group of 11 cases without demonstrable organic digestive tract disease shows 6 cases under 60 years of age, and seemingly justifiably classed as non-senile, in

TABLE V

6 cases under 60 years age with G. I. symptoms and no demonstrated organic digestive tract disease

Age	Sex	Duration of Symptoms
34	F.	2 years
59	F.	1 year
58	F.	6 years
58	M.	20 years
43	F.	18 years
51	F.	20 years

whom there were gastro-intestinal symptoms. This group is particularly important in attempting to appraise an association of gastro-intestinal symptoms with generalized osteoporosis. Age and sex incidence and duration of symptoms of this group are given in Table V.

A careful review of the symptomatology of these 6 cases shows them all very similar in character. Anorexia, feeling of fullness in the abdomen with or

without gaseous cruetation, vague abdominal pains, vague unqualified indigestion, nausea with occasional vomiting, and constipation were complaints in all cases, and these symptoms seemed to vary somewhat from time to time.

Chronic cholecystitis, irritable colon or spastic constipation, and gastric neurosis were tentative diagnoses offered at some time or other in the course of these cases before the osteoporosis was discovered. Available dietary history did not reveal any definite tendency to taking of a calcium deficient diet, but it was interesting that almost universally there was a suggestion of intolerance of fatty foods. However, there was a suggestion of either insufficient calcium intake or inefficient absorption of calcium in two cases which responded symptomatically to the administration of 6 grams of dicalcium phosphate with viosterol (3600 units U.S.P.) daily, showing measurable replacement of calcium in the skeleton within two to three weeks as determined by a standardization method developed by Dr. George C. Henny of the Department of Radiology to be reported elsewhere. How complete and permanent such therapy will be in replacing calcium and ameliorating symptoms remains to be seen, and, of course, caution should be urged in

TABLE VI

Case No.	Blood Calcium	Blood Phosphorus	Blood Phosphatase
3	10.7	2.96	2.52
7	9.0	3.4	
8	11.0	2.0	
11	10.3	3.6	
15	10.0	3.9	7.0
18	11.8	4.6	
21	9.6	3.3	
23	12.9	7.9	
24	9.1	4.4	1.4
25	9.5	4.5	4.0

interpreting the gastro-intestinal symptoms as due to calcium deficiency.

Blood serum calcium and phosphorus were determined in 10 of the cases having gastro-intestinal symptoms, and phosphatase was determined in 4 cases. These are given in Table VI, and show essentially normal values except in one case in which both calcium and phosphorus were somewhat elevated, and in another case the phosphatase was slightly elevated. In 5 of the 6 cases under 60 years of age having gastro-intestinal symptoms without demonstrable organic digestive tract disease, blood serum calcium and phosphorus determinations were available and all within normal limits.

Gastric analyses were not available, so the question of whether gastric acidity might be etiological could not be answered. However, 19 cases of pernicious anemia, all with gastric analysis and the characteristic acidity, were studied for generalized osteoporosis and only 1 case showed it to be present.

As further controls, 50 recent cases of chronic cholecystitis as diagnosed by clinical history and physical examination, and non-functioning gall bladder

by X-ray (oral method) were studied, several of these being confirmed by operation, and only 1 case of generalized osteoporosis was found. Also 23 cases of chronic colitis of long standing were studied and no cases of generalized osteoporosis found.

SUMMARY AND COMMENT

Fifty cases of generalized osteoporosis in the adult were studied and 22 were found to have gastro-intestinal symptoms. None of these cases had the changes in blood chemistry of hyperparathyroidism. It is obvious, therefore, that severe generalized osteoporosis may be and often is without gastro-intestinal symptoms. This type of osteoporosis, with or without gastro-intestinal symptoms, is predominant in the female. Some of the cases were necessarily considered to be senile osteoporosis because of the age. There was no obvious cause of the osteoporosis, such as long standing hyperthyroidism, chronic steatorrhea, or chronic diarrhea. When organic digestive tract disease was present in those cases having gastro-intestinal tract symptoms, chronic cholecystitis was the most common diagnosis. A careful review of 6 cases under the age of 60 having gastro-intestinal symptoms but no demonstrable organic digestive tract disease, showed a marked predominance of females, the duration of the symptoms generally to be a number of years, and the gastro-intestinal symptoms consisted of anorexia, feeling of fullness in the abdomen, with or without gaseous eructation, vague abdominal pains, vague unqualified indigestion, nausea with occasional vomiting, and constipation. It seems likely these gastro-intestinal symptoms are not caused by osteoporosis, but rather that patients, particularly women from 45 to 60 years of age, having such symptoms of long duration may have some nutritional deficiency or disorder of calcium absorption resulting in chronic or intermittent negative mineral balance. Calcium balance studies in well selected cases, to be reported later, should add to our understanding of this type of osteoporosis.

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DISCUSSION

DR. JOHN L. KANTOR (New York): I should like to take this opportunity to discuss several papers together,

Dr. Althausen's yesterday, Dr. Wilbur's this morning, Dr. Mackie's and Dr. Brown's.

I think we are now in a position to look at this subject in a broad way. In my opinion, it is not so important to stress the fact that we are dealing with a deficiency disease here as it is to emphasize that we have a failure of absorption. It isn't that these patients haven't been getting vitamins but they are "funny" kind of people, who cannot absorb vitamins, and I think Dr. Mackie's chart confirms this thought. He didn't show much difference in absorptive power between the ulcerative colitis group, the ulcer group, and miscellaneous ward patients.

One can get at this inability from X-ray studies such as Dr. Mackie and others have done, or from a study of the fat in the stools. It is the fat that is the hardest thing to absorb and the easiest to pick up, provided tests are available. Unfortunately, these tests are not done in most institutions, at least on a quantitative basis.

(Dr. Kantor then showed a series of slides illustrating the roentgen diagnosis of idiopathic steatorrhea. The chief changes were in the small intestine where the mucosal pattern showed a loss of the valvulae conniventes (so-called "moulage sign") and there was segmental dilatation and occlusive spasm).

DR. ANDREW C. IVY (Chicago): I should like to ask Dr. Brown if he studied the rate of gastric emptying in any of the patients. The results we reported from our Laboratory on the occurrence of homogeneous osteoporosis in gastrectomized animals were due to anacidity plus other factors. These animals had lost the reservoir function of their stomach, and the food was rapidly passed through the upper part of the intestine where normally most of the calcium is absorbed; so if a patient has achlorhydria plus a rapidly emptying or a dumping stomach, the presence of the two factors would be more likely to produce a disturbance of calcium metabolism than achlorhydria alone.

Another factor we need to keep in mind is that achlorhydric patients tend to manifest a post-cibal acidosis, because while they are not secreting acid in the stomach, they are secreting alkaline bile and pancreatic juice which obviously tends to produce an acidosis; and presence of an acidosis when calcium is being absorbed, tends to decrease calcium retention. It is generally known, one can decalcify bone by maintaining an acidosis over a long period of time.

I might add that we have seen a patient with homogeneous osteoporosis and multiple fractures which resulted three years after a radical gastric resection.

DR. THEODORE L. ALTHAUSEN (San Francisco): Our experimental work on the intestinal exchange of calcium in rats supports the findings of Drs. Brown and Vogel. In attempting to discover the cause of the negative calcium balance in patients with hyperthyroidism, which in severe cases may end in osteoporosis, we found that the intestinal absorption and excretion of calcium were normal in hyperthyroid rats. Since the fecal output of calcium is approximately doubled in hyperthyroid rats, we conceived the idea that increased intestinal motility may be an important factor. This was shown to be correct when administration of castor oil or of cascara in very small doses, insufficient to produce diarrhea in any of the animals, resulted in twice the normal output of calcium in the feces of normal rats fed a calcium-free diet. Conversely, administration of morphine to slow intestinal peristalsis reduced the fecal calcium of hyperthyroid rats almost to normal.

Our findings not only explain the existence of a negative calcium balance in hyperthyroidism in spite of a normal blood calcium level, but also explain the lack of loss of calcium through the feces in patients with hyperpara-

thyroidism who do have an increased level of calcium in the blood.

Meulengracht recently described the occurrence of osteomalacia of the spine due to chronic misuse of cathartics.

DR. CHARLES L. BROWN (Philadelphia): I have no comment to make in closing. In answer to Dr. Ivy's question, two of these cases did show what might be considered as an increased rapidity of emptying of the stomach.

The Role of the Circulation in the Production of Peptic Ulcer

By

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and

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ALTHOUGH no single etiologic factor has been established as the cause of peptic ulcer, analysis of conditions under which ulcer occurs, suggests that the local lesion is mediated through alterations in circulatory efficiency. Such alterations may be mechanical or quantitative as in cardiovascular disease, nutritional or qualitative as in metabolic disturbances, anaemia, blood dyscrasia and infections, or functional or vasomotor as the result of disturbances in the sympathetic nervous system. But regardless of the mode of production of the circulatory insufficiency, the ulcer is the result of local alteration of nutrition of the stomach wall.

The anatomic peculiarities of the vascular bed of the stomach (1) and its rich vasomotor innervation, predispose this viscus to local deficiencies in blood supply. However the production of gastric ulcer by experimental blood protein depletion or plasmapheresis (2) and by repeated injections of pitressin, (3) suggests that the gastric ulcer is not necessarily an isolated nutritional disturbance of the stomach wall, but part of a generalized circulatory insufficiency intensified in focal areas of the stomach because of the anatomic structure of its intrinsic circulatory bed and its neural peculiarities.

With the purpose of evaluating the role of circulatory insufficiency in the mechanism of gastric ulcer, we have analyzed a series of 161 cases which at post mortem presented acute lesions of the gastric mucosa. These cases represent a cross section of the autopsy material of a general hospital. Although the cause of death varied widely, the cases can be divided into four primary categories.

CHART I

Etiologic factors in acute lesions of the gastric mucosa

161 Cases

Cardiovascular disease	77
Metabolic disturbances	52
Primary cerebral disease	18
Anaemia, blood dyscrasia, and chronic infection	14

CHART II

Etiologic factors in acute lesions of the gastric mucosa—cardio-vascular disease (quantitative circulatory insufficiency)

77 Cases

Hypertensive cardio-vascular renal disease	27
Chronic myocardial degeneration	23
Essential hypertension	11
Chronic rheumatic valvulitis	10
Syphilitic cardio-vascular disease	4
Congenital heart disease	2

CHART III

Etiologic factors in acute lesions of the gastric mucosa—metabolic disturbances (qualitative circulatory insufficiency)

52 Cases

Hepatic insufficiency	23
B ₁ avitaminosis (1)	14
Diabetes mellitus	8
Chronic metallic poisoning (2)	7

(1)—Chronic alcoholism 10, chronic vomiting 4; (2)—Lead poisoning 6, arsenic poisoning 1.

CHART IV

Etiologic factors in acute lesions of the gastric mucosa—primary cerebral disease (vaso-motor circulatory insufficiency)

18 Cases

Expanding intracranial lesions (1)	13
General paresis of the insane	2
Multiple sclerosis	2
Chronic traumatic encephalopathy	1

(1)—Primary cerebral abscess 3, brain tumor 10.

CHART V

Etiologic factors in acute lesions of the gastric mucosa—anaemia, blood dyscrasia and chronic infection (qualitative circulatory insufficiency)

14 Cases

Secondary anaemia	9
Chronic infection (1)	4
Blood dyscrasia (2)	1

(1)—Lung abscess 2, empyema 1, pulmonary tb. 1; (2)—Hemorrhagic disease of the new born 1.

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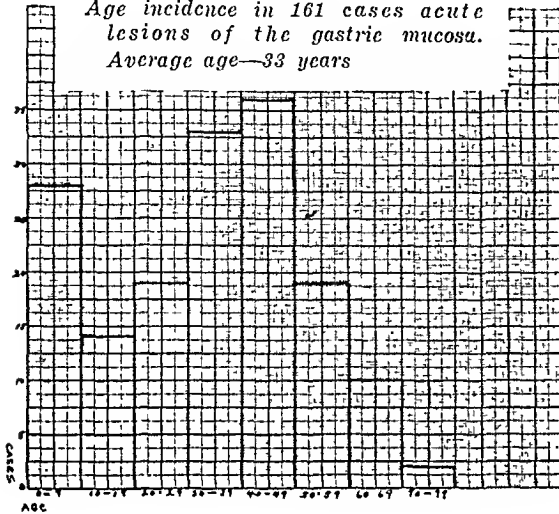
The Philadelphia General Hospital, Philadelphia, Pa.

Read at the Annual 1935 Session of the American Gastro-Enterological Association at Atlantic City.

In order to facilitate comparison with clinical cases of ulcer, and to minimize the cardiovascular insufficiency of older age groups we have chosen our cases predominantly from the younger age levels. The frequency table shows fair agreement with that of the incidence of clinical cases of ulcer. The average was 33 years, and 80% of the cases were under 50 years of age.

TABLE I

*Age incidence in 161 cases acute lesions of the gastric mucosa.
Average age—33 years*



The following types of acute lesions of the gastric mucosa were found in this series.

CHART VI
Acute lesions gastric mucosa
161 Cases

Type	Cases	Per Cent
Perforations	16	10
Mucosal hemorrhages	25	16
Macroscopic ulcers	41	24
Microscopic ulcers	40	25
Microscopic erosions	16	10
Severe congestion	23	14

Although the lesions of the gastric mucosa were acute, histologic study, using differential stains demonstrated that in the area of the mucosal lesion all the layers of the stomach wall were involved. Further, although the mucosal degenerations were acute, the alterations in the deeper layers were essentially chronic. In no area examined was the mucosa alone involved. The mucosal alterations were invariably superimposed upon chronically degenerated submucosal and muscular layers. Conversely, it was possible to demonstrate areas adjacent to the acute mucosal lesions where normal healthy mucosa had regenerated despite chronic alterations in the deeper layers.

The wedge shaped pattern in the acute mucosal lesion and the picture of chronic alteration in the deeper layers suggests that vascular deficiency of a

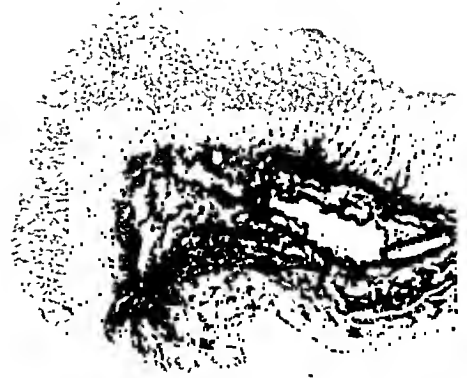


Fig. 1. Focal erosion (ischemic necrosis) of distal portion gastric mucosa. Fibrosis muscularis mucosae. Varicose dilatation of vessels of submucosa due to chronic stasis. Atrophy and fibrosis muscular coat.

persistent or recurrent type had existed. The muscle coats were oedematous, decreased in thickness and showed metamorphic basophilic staining with the trichrome stain. There was marked proliferation of connective tissue reticulum between both the individual muscle fibres and the circular and longitudinal coats. In the submucosa, with its vascular plexes, the evidence of prolonged stasis was most marked. The veins were tortuous, almost to the point of varicosity, while both veins and arteries showed fibrosis of the walls. The entire coat was increased in width, and its loose areolar structure was replaced by dense, structureless hyalin material, or in many cases, by fibrous connective tissue. This resulted in a fusion of the layers of the stomach wall. In practically all cases the muscularis mucosa had been replaced by connective tissue which showed focal proliferation at the base of the mucosa and extended along the trabeculae between the gastric glands. Thus, although the mucosa has no independent blood supply, histologic study showed that



Fig. 2. Focal ulcer involving entire depth of mucosal layer (ischemic necrosis). Fibrosis of deeper structure with atrophy of muscular coat.



Fig. 3. Necrosis and desquamation of mucosa at right (acute ulcer). Varicose dilatation of submucosal vessels. Muscular layer replaced by connective tissue except for small area at extreme right.

normal or acutely altered mucosa may be present when the deeper structures, which are closer to the stem artery, show the effects of prolonged or repeated periods of circulatory stasis.

The apparent paradox can be explained by the fact that regeneration of the mucosal coat following repeated focal destruction can occur at the same time that progressive degenerative changes are taking place in the deeper structures which possess less potentiality of regeneration.

In order to present the relative changes in the entire thickness of the gastric wall, we have utilized microscopic-sized mucosal lesions for our illustrations. However, it is possible to reconstruct the same progress of events in the acute macroscopic ulcers.*

*The trichrome stain used to demonstrate the sections is original with Miss Edna Beyer, technical assistant in the division of neuropathology of the Philadelphia General Hospital. Connective tissue, collagen and mucus stain blue, while gastric glands stain red. Muscle in its normal state takes the red stain, but becomes increasingly basophilic as degeneration progresses. To be published in *Am. J. Clin. Path.*



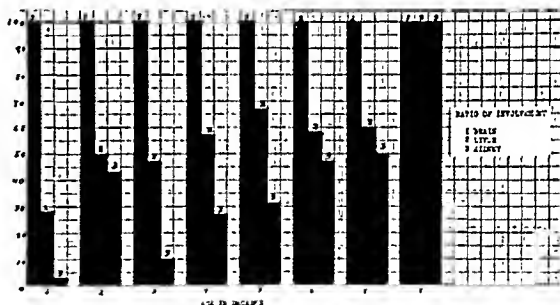
Fig. 4. Hyalinization of submucosal layer. Atrophic changes in muscular coat. Mucosa is atrophic and shows focal ischemic degeneration at one point. Complete fusion of all coats. This is probably an irreversible stage.

Although the nature of these gastric lesions strongly suggests an insufficiency of the circulation, study of the stomach lesion itself gives no clue whether this condition is a local one or due to general insufficiency with its frequently resulting widespread stasis. For this reason, using the same criteria employed in the histologic study of the gastric lesion, namely degeneration of parenchymatous cells with proliferation of connective tissue, we attempted an evaluation of the presence of generalized circulatory insufficiency by examining the brain, liver and kidney in those cases presenting acute lesions of the gastric mucosa. The evidence of impaired circulation found in these organs would make it reasonable to assume that the anatomically inadequate blood supply and the intrinsic vasomotor innervation of the stomach do not cause the gastric lesion through local disturbances alone, but merely intensify a local picture incident to the generalized insufficiency of the circulation.

As might be expected, the brain with its functional dependence upon the integrity of the systemic circulation showed the earliest reflection of generalized circulatory insufficiency. In 37% of the series, it was the only organ, except the stomach to show degenerative changes. On the other hand, there was no case with a gastric lesion which did not show brain involvement as well. The liver, with the same blood supply as the stomach, was involved in only 53% of the cases. Lesions incident to chronic stasis were present in the kidneys in 38%. The graph demonstrates that the ratio of brain, liver, kidney involvement increases with age.

TABLE II

General circulatory insufficiency in 161 cases of acute lesions of the gastric mucosa



CONCLUSION

From histologic study of 161 cases of acute focal lesions of the gastric mucosa, we would conclude.

1. Regardless of etiology, focal gastric lesions are the result of chronic circulatory insufficiency to all the structures of the gastric wall.

2. Such circulatory deficiency is part of a generalized insufficiency intensified by intrinsic vascular peculiarities of the stomach, of an anatomical or vasomotor nature.

3. Generalized circulatory insufficiency may be established through quantitative, qualitative or vasomotor alterations in the circulatory system.

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DISCUSSION

DR. CHARLES M. WILHELMJ (Omaha): I want to congratulate Dr. Boles and his colleagues for this very important and very intriguing study.

The facts, I think, were clear enough from their slides. Of course, what is back of these changes is open to speculation. I should like to point out that a similar acute vascular lesion is found very often in dogs under a variety of conditions. For instance, we find that in animals dying from distemper, adrenal insufficiency, obstructive jaundice, or total biliary fistula, these types of changes are very likely to occur, as a matter of fact, almost always. I have also seen similar lesions in animals dying from foreign protein shock.

It is well known among physiologists, at least, that if the causative factor is removed, all of these acute mucosal hemorrhagic vascular lesions will heal and heal quite promptly; for instance, if the biliary obstruction is relieved, or there is removal of the total biliary fistula, they will clear up, but if the causative agent continues to exert its influence, many of these acute lesions will go on to chronic lesions such as we see in total biliary fistula, obstructive jaundice, and other conditions.

I think that in the present work there are two very important findings: First, the evidence of repeated insults. These were not acute, as you saw from the degenerative change or changes going on in the deeper layers, where the muscular layers have been almost completely replaced by fibrous tissue, so these things were coming repeatedly, which gives us one of the factors which may lead to chronicity.

The second thing which I think is of importance is the fact that they found similar lesions in the brain and the liver, lesions at least that suggested that the same changes were going on.

Now, that the nervous system may be involved in the production of chronic ulcer is more or less generally accepted, although it is very hard to prove it experimentally.

Of course, the lesions which have been pointed out by Cushing and by others, and also the experimental lesions produced after hypothalamic injury, suggest that the nervous system is involved. The essayists also told me they had found pathological changes in the vagus nerves and the sympathetic ganglia.

The changes in the liver, I think, are very important. I am coming more and more to the belief that the liver may be a very important factor in the genesis of chronic peptic ulcer. It is a difficult thing to prove, but more and more evidence is pointing to the liver as one of the important factors.

They found lesions in the liver, so that they have here three things which you might expect finally to lead to chronic ulcers in certain of these patients:

- (1) Repeated insults, not just one, but repeated.
- (2) The nervous system was involved, which might lead eventually to hyper-secretion, spasm, and so forth.
- (3) The liver was involved, which might bring in what I personally believe to be an important but, at the present time, an unknown factor. I wish to congratulate Dr. Boles and his colleagues upon this very significant work.

DR. RUDOLF SCHINDLER (Chicago): May I ask one question, Dr. Riggs? How did you differentiate these acute lesions you saw in autopsy material, from the well known postmortem changes? I could not get this point.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): Any contribution that may throw light on the genesis of acute and chronic gastric ulcer is certainly welcomed by this Society. I am of the opinion that the acute lesion is frequently the basis for gross bleeding without any other

manifestations. I hope that the essayist will describe the technic of tissue staining, as the slides which they have shown are beautiful in this respect. I think that Doctor Necheles will agree with me.

Doctor Necheles: Yes.

Doctor Eusterman: We may also have to revise our conception of the gross pathology of chronic gastric ulcer in view of this report, because the older school has taught that an ulcer is only chronic when it reaches the depth of the muscular layer or serosa. The ability of the mucosa to thoroughly regenerate itself is a well established fact, as is borne out by pathologic studies for years past on healed acute and chronic gastric ulcer.

I am curious to know if the lesions under discussion give rise to any symptoms during the life of the individual. To what extent such acute lesions can give rise to lesions other than gross and occult bleeding, and their causative relation to chronic ulcer, is not yet clear. In recent years the thought has been advanced in sundry parts of the scientific world that we must forget about acute ulcer being the precursor of a chronic one before we can learn anything etiologically about the latter. The causative role of vascular nature is refuted by many pathologists, notably Aschoff, although we know that to vascular spasm von Bergmann attributes fundamental importance. Finally, I wish to state that while chronic ulcers are frequently seen in association with disease of the central nervous, cardiovascular, renal and endocrine systems, which may or may not give rise to very marked disturbances, such lesions in association with disease of the biliary tract are much less frequent than one would expect. At least from my clinical experience, the relationship of hepatic disease to the genesis of ulcer appears to be a very doubtful one.

DR. ANDREW C. IVY (Chicago): Some have suggested that they believe the cause of these acute lesions is vomiting prior to death; that is, the spasm of the pyloric antrum causes a rupture of the blood vessels, hemorrhage into the mucosa which is followed by digestion. This mechanism can cause acute ulcers in animals in the laboratory; it is very easily demonstrated; but vomiting and pylorospasm has not been proven to be a cause of acute lesions in the stomach of man.

I believe that the essayists could make a contribution, since they observe a difference in the distribution of acute lesions depending on the cause of death, by going into the history of their patients and ascertaining if they vomited prior to death.

I noted that cardiac insufficiency heads the list as a possible related cause of these acute lesions. We frequently administer digitalis to such patients, and we know digitalis is a gastric irritant and causes vomiting.

DR. HEINRICH NECHELES (Chicago): I am particularly happy about this paper because I feel that it confirms some of the results reported yesterday by Dr. Schindler and myself. About 15 years ago Mueller and Heimberger showed that in all ulcer patients whom they examined, tortuous capillaries were present in the skin, the lips and in the gastric mucosa; this was such an amazing finding that I was surprised that it never had been repeated, and wanted to do it myself. I am particularly happy to see that Dr. Boles has been able to attack this question from quite another angle, and much more profoundly than Mueller.

The old question whether ulcer is due to local or to general disturbances, is brought nearer to a solution by Dr. Boles' work, which points definitely to generalized disturbances in circulation in ulcer patients.

You may not have read a recent paper by Dr. Babkin in which he proposes that histamine may play a rôle in the formation of ulcer. We have proposed that acetylcholine

plays a rôle. Both theories assume disturbances in the vascular supply of the stomach, especially in areas with end vessels, where there are few or no collaterals, areas which are much more prone to devitalization in case of spasm or of stasis; and these regions show the greatest incidence of ulcers; namely, the lesser curvature and the duodenal bulb.

It is, of course, a very difficult question to decide whether these numerous and rather general pathological findings are coincidental with ulcer or causal to ulcer.

One thing impressed me very much, and that is the very distinct appearance of stasis and tortuosity of the capillaries, and I think the beautiful technic, on which I want to congratulate Dr. Riggs, brings that out most clearly.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): Twenty-five years ago and for many years thereafter, one of our members, Fenton B. Turck, presented to this Association reports of his observations on the production of stomach ulcers in animals, during the course of his experiments on shock. Extracts of dead tissue of the animals were injected intravenously into the same or other animals of the same species, producing all the manifestations of shock, including the focal necrosis in various organs, such as brain, liver and stomach. He pointed out that when these lesions occurred in the stomach they were pathologically identical with those of lesions which we had been calling chronic gastric ulcers, even though it had taken only a matter of minutes to produce them. He called the factor producing shock and these lesions at first shock toxin, then cytolsin and finally cytost. At one of our meetings I pointed out that such a factor would be present in the dead tissue occurring at the site of a so-called focal infection and might account for the relationship between such infections and peptic ulcers. Later, Lewis Gregory Cole presented to us his proofs that peptic ulcers are acute, and that, barring complications, they heal rapidly, often leaving scars so fine as to be recognizable only microscopically. Pathologists have called attention to the frequent finding at autopsies of multiple healed lesions which must have been peptic ulcers.

My conception of an ulcer is that it is an acute process, healing rapidly and spontaneously, and not becoming chronic unless its base has penetrated or almost penetrated the serosa, producing marked infiltration of the wall and perigastric or periduodenal adhesions and induration. The lesion then becomes a chronic process, producing deformities and physiological disturbances usually requiring surgical intervention.

My feeling is that this report of Dr. Boles and his associates is one of the most important events of this meeting. Dr. Boles has again scored by reporting on pathological material, of which we are getting too little these days. His findings, in my opinion, constitute another step in the confirmation of the theories of Turck and Cole.

DR. RUSSELL S. BOLES (Philadelphia): Mr. President, I want to express the very deep appreciation of Dr. Riggs, Dr. Griffiths, and myself, for this very generous discussion.

I wish I had time to answer all the discussers in detail, but I will have to refer briefly to their questions and, if there is anything further I shall be glad to see them later.

Dr. Schindler asked how the histologic picture differs

from that of acute focal post-mortem necrosis. I think the stain speaks for itself in this respect. Certainly the chronic changes noted in the deeper layers are not the result of post-mortem degeneration. These same changes were observed by Nedzel in his experimental work in dogs.

Dr. Eusterman asked if the patients had any symptoms of ulcer. We have not completed a clinical survey of the cases and hope to do this later. We can say at this time that most of the patients did not present the conventional symptoms of chronic peptic ulcer.

In answer to Dr. Ivy's question, I might say that less than 10 per cent had any history of vomiting.

Dr. Andresen mentioned that an ulcer doesn't become chronic except under certain circumstances. We believe that it does not become chronic until there is absolute incapacity of the mucosa to regenerate itself because of the chronic degenerative changes in the deeper layers that we have demonstrated.

This paper, for me, holds considerable interest because of the clinical implications that may be derived from it. To begin with, I think it is becoming increasingly obvious that the solution of this question of peptic ulcer depends quite definitely on a broad, general approach to it. This is particularly important in formulating an intelligent method for the medical and especially the surgical management of the disease.

"Peptic ulcer," unfortunately to me is a very unscientific and misleading term to use to designate this disease. We must get a different name for it because the term "peptic ulcer" concentrates attention primarily on a local lesion in the stomach. We wouldn't think of doing this, for instance, in diabetes. We don't concentrate our attention on the ulcer of the toe in diabetes, or in Buerger's disease, or in arteriosclerosis or in other conditions in which an ulcer is simply an end result.

Another thing that impresses me as a result of this study is the possibility that there may be a common denominator not only in peptic ulcer disease, as I like to think of it, but in such similar conditions as coronary artery disease, and thrombo-angiitis obliterans, or Buerger's disease; in other words, in diseases of the peripheral or end-arteries in various other structures.

The approach, then, I think, as I said before, must certainly be from a broad, general point of view. We must stop studying ulcer as a local lesion. We must begin wondering about the serum proteins. Why does a patient with ulcer have a high hemoglobin and red cell count? What is the viscosity of the blood? Why is it increased, as it invariably is in Buerger's disease, for instance. The symptoms and many of the sequences of events clinically and pathologically are similar in the two conditions. The nervous symptoms in peptic ulcer disease we suspect may be due to the vascular stasis that occurs in the brain and the neural structures.

That the circulatory factor in ulcer are important is suggested by the effect on the lesion of certain drugs—tobacco for instance. Why is tobacco bad for ulcer patients? Is it because it stimulates hypersecretion or increases acidity, or because of the vasoconstrictor effect on the blood vessels at the site of the lesion? In Buerger's disease one can observe within twenty-four hours a change in the appearance of an ulcer of the foot following a restriction of smoking. Pilocarpine exhibits a similar effect experimentally.

Massive Hemorrhage from Peptic Ulcer*

A Study Based on Vital Statistics of the City of Seattle During Four Years
and on Personal Experience in Private Practice

By

JOHN MINOR BLACKFORD, M.D.

and

WILLIAM S. COLE, M.D.

SEATTLE, WASHINGTON

PERUSAL of recent literature (2, 4, 6, 7, 8, 10, 11, 14, 15, 17, 23) shows remarkable variations in mortality from massive hemorrhage from peptic ulcer as reported from large charity hospitals. Most authors reporting from such institutions give mortality rates varying from 10 to 30 per cent. On the other hand, Finsterer (14) of Vienna, reports a mortality of 5 per cent in emergency surgery on bleeding ulcer. Lahey expects a 5 per cent mortality from bleeding ulcer. Hurst (13) reports 4.8 per cent mortality from Guy's Hospital, and states, "The danger of hemorrhage from peptic ulcer has been greatly exaggerated in a number of recent papers." He feels that in private practice the mortality is between 1 and 3 per cent.

Two years ago we (18) presented a study of our private patients suffering from gastric hemorrhage from peptic ulcer, together with remarks on vital statistics and peptic ulcer. We showed that the great majority of deaths from hemorrhage occurred in older patients—a point not previously emphasized. Allen (17) simultaneously and independently confirmed our conclusions that the age of the patient with bleeding ulcer is the most important factor in prognosis, and that in the age group above 50 years the mortality rate is approximately 30 per cent. Since that time a number of writers have remarked on the higher mortality in older people. Rankin (24) is the most recent advocate of emergency surgery for massive hemorrhage from peptic ulcer in persons past 50 years of age. Pfeiffer (22) is another of those recently advocating surgical treatment in older people; and other writers are now advising surgery for older patients suffering from massive hemorrhage.

Surgical treatment of hemorrhage has been championed by Finsterer (14), who feels that immediate operation for bleeding ulcer is always indicated and that no patient should be refused immediate operation. At the other extreme, Hurst (13) feels that operation for hemorrhage is rarely if ever indicated. A review of articles for several years just past reveals, however, that emergency surgery has rarely been undertaken. Repeatedly the idea is expressed that those patients whose illness will result fatally cannot be separated by clinical evidence from those who will survive; that emergency surgical mortality is much higher than that of medical supportive treatment; and that hence we should not increase mortality by emergency attempts at surgical control of hemorrhage from peptic ulcer.

STATISTICAL FALLACIES

Two years ago we were profoundly impressed with the difficulty of correlating statistical studies. Some authors have figures on all admissions for hemorrhage, others include only those severe cases which we call massive hemorrhage. Some record only cases with hematemesis. Some authors include and others exclude cases operated upon in an attempt to save life after the failure of medical measures.

Crohn (23) has just published a scholarly presentation on gross hemorrhage from peptic ulcer in which he calls timely attention to the statistical shortcomings of ten authors, including the writer. We had become entangled two years ago in the same remarkable maze of discrepancies which he has found, and we had tried to steer clear of such difficulties.

Crohn's paper (23) has been read carefully, and he seems to have gotten into as much trouble statistically as anybody else. Study of his tables shows that he has included 40 anastomotic bleeding ulcers with no deaths. Anastomotic ulcers are hardly, in our judgment, to be classed with unoperated ulcers. Excluding these his mortality for gross bleeding from peptic ulcer is raised from 6.5 per cent to 8 per cent; and if, as he states, two-thirds were severe hemorrhages, then his mortality from massive hemorrhage is 12 per cent. He excludes 75 cases operated upon for hemorrhage, though he writes, "35 patients over the age of 45 were operated, and 15 succumbed (46 per cent)* . . . Most of them represented the futility of medical means and conservative patience." There were 5 other deaths following operation in his series, presumably younger patients. We have found it impossible to confirm the arithmetic of percentages as shown on his charts, for the arithmetic appears grossly in error. If the 40 anastomotic ulcers are excluded, there were 34 deaths in 251 cases of chronic peptic ulcer with active hemorrhage, or a mortality rate of 13.5 per cent for gross hemorrhage from peptic ulcer, and for massive hemorrhage it should be one-third higher, or 20 per cent. This last figure is identical with that worked out at the King County Hospital in Seattle.

CLINICAL STATISTICS

Our clinic, since 1919, has observed 1076 patients suffering from peptic ulcer. The incidence of peptic ulcer and its acute complications per 10,000 patients admitted to the clinic is approximately:

Peptic ulcer	150
Acute perforation of peptic ulcer	9
Active gross hemorrhage	16
Active massive hemorrhage	7
Fatalities from hemorrhage	1

*From The Mason Clinic.
Read before the American Gastro-Enterological Association, Atlantic City, May 1-2, 1939.

One fatality due to hemorrhage from peptic ulcer per 10,000 patients admitted to a private clinic, where gastro-intestinal cases are common, prompts the observation that many physicians in general practice may go through a busy lifetime without seeing a fatality from massive hemorrhage from ulcer.

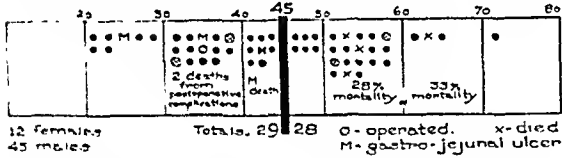
Tabulation of our histories shows that hemorrhage is recorded in 208 patients, or 19 per cent of all patients with peptic ulcer. Active hemorrhage has caused 113 patients to consult the clinic. Half of these patients were having only moderate loss of blood, evidenced by melena or hematemesis in moderate amount, without serious symptoms. We have classified such cases as *gross hemorrhage* and have not included them here.

The other half were suffering from serious blood loss, with alarming symptoms of exsanguination. These cases have been classified as *massive hemorrhage*. The classification of hemorrhages as moderate or massive must be a matter of clinical judgment. We diagnose *massive hemorrhage* when we find evidence of large loss of blood, with pallor, weakness, sweating, and prostration. Blood examinations in the first 48 hours of severe hemorrhage are of little value in estimating the amount of blood loss.

Careful study of case histories reveals, then, that only half of our patients with active gross hemorrhage were severely ill; therefore, our mortality percentages for massive hemorrhage should be halved if they are to be compared with those of authors who have listed mortality percentages based on *all* their cases of active gross hemorrhage.

THE MASON CLINIC
57 Active Massive Hemorrhages
Peptic Ulcer

EXCLUDING 56 CASES GROSS BUT NOT MASSIVE HEMORRHAGE



SEVERITY OF PAST
ULCER HISTORY

Grade	I - 12	
	II - 18	30
	III - 19	
	IV - 8	27

ULCER SYMPTOMS
AT TIME OF
HEMORRHAGE

39 quiescent
18 active

*5 OF 6 DEATHS FOLLOWED FIRST HEMORRHAGE.
Chart 1

MASSIVE HEMORRHAGE

As already stated, and as shown on Chart 1, 57 of our 113 cases of active gross hemorrhage were classed as massive hemorrhage. These patients all bled profusely and developed the classical signs of severe hemorrhage, and 6 older patients bled to death, including 2 exsanguinated patients who were operated upon after prolonged attempts at control of hemorrhage by medical means.

Further analysis shows that of those operated upon for control of hemorrhage, 3 deaths occurred in patients under 45 years of age; 1 was bleeding from a gastrojejunal ulcer, and 2 patients died from complications following operation but not from hemorrhage.

The death of 3 younger and 6 older patients gives a gross mortality of 15 per cent for massive hemorrhage from ulcer. The 6 deaths of patients above 45 years were due to exsanguination from chronic bleeding peptic ulcer, a mortality from hemorrhage of 11 per cent. If this 11 per cent be halved, since half of our cases of gross hemorrhage were not considered as massive hemorrhage, the figure of 5 per cent used by several writers as the mortality from hemorrhage in private practice is approximated. Of the 6 fatalities in older patients, 5 occurred during their first hemorrhage.

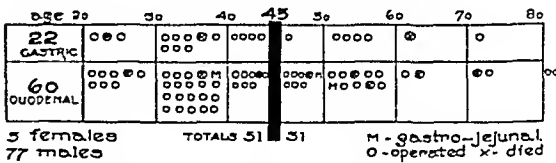
The histories of these patients with critical hemorrhage have been carefully tabulated in an attempt to evaluate the severity of the past symptoms. More than half gave histories of relatively mild symptoms. Neither chronicity, severity, age, nor sex has given a clue as to which ulcers are likely to bleed. A study of the histories also shows that at the time of massive hemorrhage only one-third of the patients were having severe symptoms due to ulcer. Two-thirds of the massive hemorrhages occurred during relatively quiescent periods.

On charting ages by decades, it is apparent that half of all 208 patients with gross active hemorrhage—mild and severe—admitted to our clinic were below 45 years of age. If the time of the first gross hemorrhage is charted from 208 histories, 60 per cent were under 45 years of age when the first hemorrhage occurred.

MASSIVE HEMORRHAGE AND ACUTE
PERFORATION

The Virginia Mason Hospital has, since 1920, admitted 82 patients suffering from acute perforation of peptic ulcer, and all were operated upon. Massive hemorrhage accompanied acute perforation in four instances only, and all four survived operation. Chart 2 gives the ages by decades of 82 patients admitted to the hospital for acute perforation, and shows that 51 of the patients were under 45 years of age. By decades, we find that 28 patients were in the thirties, 21 were in the forties, and 14 in the fifties. Two patients past 80 years of age recovered following operation for perforation.

THE MASON CLINIC
82 Acute Perforations
Peptic Ulcer
(11 DEATHS)



55 PERFORATIONS DURING QUIESCENT SYMPTOMS
27 PERFORATIONS DURING ACTIVE ULCER SYMPTOMS
4 PATIENTS HAD A PREVIOUS DIAGNOSIS OF ULCER
*2 OPERATED AFTER 24 HRS.

MORTALITY	
under 45 yrs.	9.8%
over 45 yrs.	19.3%
gross	13.4%

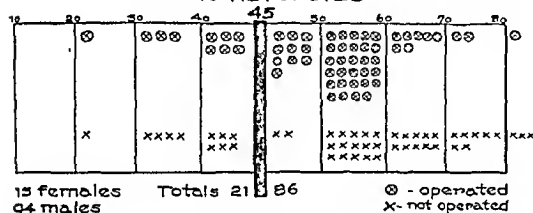
Chart 2

Eleven deaths followed operation, a gross hospital mortality of 13.4 per cent. The visiting staff of the

hospital operated upon 21 patients, all within 24 hours, with 4 deaths, mortality 20 per cent; The Mason Clinic operated upon 61 patients, with 7 deaths, mortality rate 11.5 per cent. The Clinic mortality for 56 acute perforations of peptic ulcer operated upon within 24 hours is just under 9 per cent. The Clinic cases include 3 patients with gastrojejunal perforation who recovered and 2 operated upon more than 24 hours after perforation who died.

Only 4 patients admitted for acute perforation knew that they had peptic ulcer before the perforation occurred, indicating the rarity of a severe ulcer history in cases that perforate. Two-thirds of the acute perforations occurred in periods in which ulcer symptoms were quiescent.

1935-1938 SEATTLE VITAL STATISTICS 107 Deaths Acute Perforations Peptic Ulcer 46 AUTOPSIES



NO ACUTE PERFORATED GASTRO-JEJUNAL ULCER NOTED
Chart 3

Chart 3 shows 107 fatalities from acute perforation, with 46 autopsies—records taken from the Vital Statistics of Seattle. Surgery must have saved many lives, for only one-fifth of the deaths occurred in persons under the age of 45, though most perforations, as shown above, occur in younger people. The vital statistics show that 49 patients died without having been operated upon. No case of gastrojejunal perforation is noted in the vital statistics. Statistics have often shown that females rarely suffer from acute perforation. Recently an incidence of 2 per cent of females is reported from Detroit (20) in a large series of acute perforations. Yet when all deaths in a large city, Seattle, are considered, we find that 12 per cent were females.

VITAL STATISTICS AND MASSIVE HEMORRHAGE

There is a satisfaction in the certainty that all deaths in Seattle must be recorded in the Bureau of Vital Statistics and therefore have been available for this study. Chart 4 shows that 216 deaths certificates give peptic ulcer as the primary or contributing cause of death during the four years of 1935 to 1938 inclusive, and that 93 autopsies (43 per cent) are recorded. The high percentage of autopsies is due to the excellent autopsy service at the King County Hospital, and to the fact that most ulcer deaths have occurred either there or in private hospitals.

These 216 death certificates have been reviewed. Seventy-two certificates recorded hemorrhage as a

*Actually 43 per cent.

1935-1938 SEATTLE VITAL STATISTICS 216 Deaths from Peptic Ulcer 93 AUTOPSIES

MASSIVE HEMORRHAGES	55
ACUTE PERFORATIONS	107
POSTOPERATIVE DEATHS	24
OTHER CAUSES	30

Chart 4

factor in the fatal outcome. It seems improbable that any physician would omit hemorrhage from the death certificate if he felt that the patient died from hemorrhage. We investigated each of the 72 cases through hospital records or through the physician who signed the certificate. The deaths from active massive hemorrhage were actually 55 in number, with 24 autopsies.

Four deaths from hemorrhage were caused by bleeding from gastrojejunal ulcers, and in two cases fatal hemorrhage occurred years after the repair of acute perforations. Seven deaths followed late operation after medical failure to control hemorrhage. Ten fatalities were in females, 45 in males. The King County Hospital had as many fatalities as the total of the private hospitals, although the County Hospital averages but half as many patients as the total of the private hospitals.

Chart 5 shows the distribution of all fatalities in age decades. The youngest patient was 39 years old,

1935-1938 SEATTLE VITAL STATISTICS 55 Deaths Massive Hemorrhage Peptic Ulcer 24 AUTOPSIES

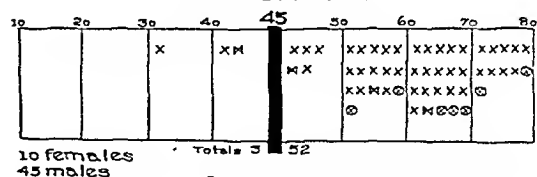


Chart 5

the next youngest 44; all others were more than 45 years old. The age incidence by decades shows 7 deaths in the forties, 16 in the fifties, 20 in the sixties, 11 in the seventies.

The rarity of fatal hemorrhage from peptic ulcer before 45 years seems proved by the fact that only 2 of 51 fatalities from chronic peptic ulcer hemorrhage occurred in patients under 45 years old, or 4 per cent of all deaths from this cause. Fatal hemorrhage from

peptic ulcer in younger people is so rare that we are probably never justified in operating on such a case as an emergency.

The percentage of fatalities from exsanguination above 45 years presents a different picture. Of 51 cases of fatal hemorrhage from peptic ulcer, 49 were in patients above 45 years. We must recognize that fatal bleeding occurs in approximately 30 per cent of serious hemorrhages in older people. The surgeon is certainly justified in attempting to stop such hemorrhages by operative measures. The internist needs surgical consultation promptly in serious hemorrhage when the patient is in the older group; and operation, when indicated, should be done promptly, not after many days' delay.

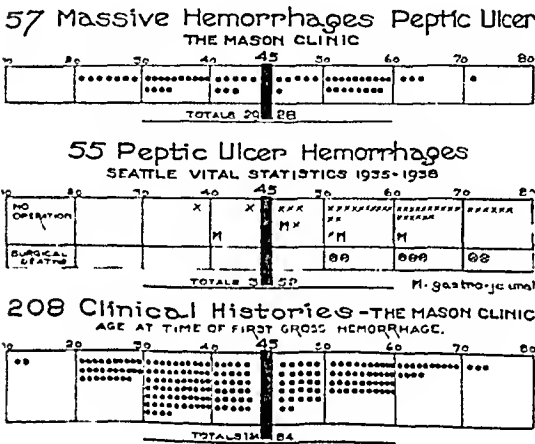


Chart 6

Chart 6 shows the remarkable contrast between the incidence by age decades of massive hemorrhage as compared with first hemorrhages from peptic ulcer. It also contrasts the fact that massive hemorrhages occur with equal frequency below and above the age of 45; yet vital statistics show that nearly all fatalities occur in the older group.

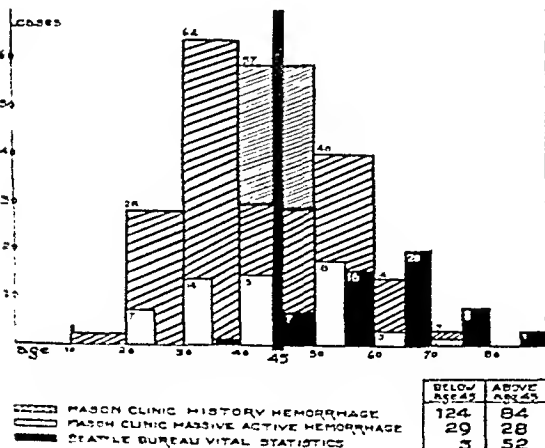


Chart 7

Chart 7 shows that the clinician sees most gross hemorrhages in the thirties, and most massive hemorrhages in the fifties. Deaths are most common in the sixties. The blocking of the chart indicates the curves of incidence of massive hemorrhage, and of all first hemorrhages, as shown by clinical histories; and of all deaths from massive hemorrhage, as shown by vital statistics.

SURGICAL TREATMENT

Our small experience in surgical treatment has not included enough cases or successes to warrant undue surgical enthusiasm. Emergency operation as a late measure has failed to save two of our patients. Two younger patients operated upon as emergencies have died from postoperative complications, but not from hemorrhage. Two other younger patients were operated upon because of exsanguination, and they survived operation; though we now suspect that they might have survived without operation.

We believe that immediate operation must be considered for older patients in every serious hemorrhage from peptic ulcer; for only thus can we hope materially to reduce a mortality rate of approximately 30 per cent in these patients. Early operation is emphasized by Finsterer (14) and Allen (17), and our small experience confirms their remarks. Delay for days to allow repeated supportive measures before operation results in almost one hundred per cent fatalities. Apparently operation must be undertaken before the blood-making ability and other reserves of the patient are exhausted. And our statistics indicate that only older patients should be operated upon.

We feel furthermore that any surgical statistics of successes in life-saving by emergency operation for hemorrhage when ages are not tabulated should be read with skepticism. Vital statistics prove that practically no deaths due to hemorrhage from peptic ulcer occur under the age of 45 years, if the surgeon can be restrained. Surgical intervention should be undertaken only on older patients, and reports of surgical successes should include the ages of the patients operated upon expressed in decades. If the surgeon can reduce the mortality materially below 30 per cent in the older group, then surgery is certainly the procedure of choice in older patients.

CONCLUSIONS

1. Vital statistics show that 4 per cent of all deaths from massive hemorrhage from peptic ulcer occur under the age of 45.
2. Vital statistics show that 96 per cent of all deaths from hemorrhage from peptic ulcer are in patients above the age of 45.
3. Vital statistics indicate that emergency surgery for bleeding ulcer is not justified on patients less than 45 years of age.
4. Early emergency surgery for massive hemorrhage from ulcer in patients above 45 years of age should save many lives.
5. No younger patients in our series of hemorrhages from peptic ulcer have died except as an immediate or late result of surgical interference.
6. The commonly quoted mortality rate of 5 per cent for peptic ulcer hemorrhage is approximately one-sixth of the actual mortality rate in older patients having massive hemorrhage from peptic ulcer.

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Results of Treatment of Massive Gastric Hemorrhage

By

ALBERT F. R. ANDRESEN, M.D., F.A.C.P.

BROOKLYN, NEW YORK

THE treatment of massive gastric hemorrhage, as evidenced by hematemesis, melena or both, has been the subject of much discussion in recent years. Twelve years ago, when I read a paper on this subject at an American Medical Association meeting, I was still under the impression that such a hemorrhage was practically never a cause of death and I could find no record of any fatality at the Long Island College Hospital during the six or seven years we had been using the treatment recommended. It was suggested merely as a method of making the patient more comfortable, shortening his stay in the hospital and making it possible to determine the cause of his hemorrhage sooner than by the older methods of treatment. Previously the treatment of hemorrhage had been pretty well standardized, consisting of at least six weeks' rest in bed, an initial period of starvation, the parenteral administration of saline, glucose or whole blood, the use of coagulants locally and parenterally, ice externally and internally, lavage with astringents or escharotics, and at times operation with no attempt at laboratory or Roentgen diagnosis for from 6 to 10 weeks. Even today such treatment, in whole or in part, is in pretty general use, although statistics have shown the relatively high mortality attendant upon it.

Essentially the treatment recommended by me consists of immediate feedings of a soothing, coagulant, nutritious food formula, the avoidance of sudden increase in blood volume or pressure, the application of warmth to the body, and resort to operation only if the hemorrhage is shown to be intractable.

It is an interesting fact that in taking histories of patients with peptic ulcer, we so often discover that they have had massive hemorrhages for which no physician was consulted, and immediately following which the patients ate as before, went back to work the next day and experienced no particular after-effects except malaise for a week or so. In recent years, Meulengracht also has called attention to this fact, and his method of treatment, based on this knowledge, has received considerable commendation because of the much reduced mortality following its use. It is quite evident

therefore, that our previous prolonged starvation periods and intensive treatments were not only superfluous, but that they unnecessarily prolonged the patient's recovery. It is therefore worth while that a brief summary of some of the factors present in a case of hemorrhage should be considered.

PATHOLOGY

Whereas nearly all patients with gross hemorrhage are suffering from a complication of peptic ulcer, it is always well to remember that hemorrhage may be the first manifestation of a carcinoma or of an esophageal varix, that recurrent hemorrhage may result from bleeding polyps or even from a severe gastritis, and that occasionally blood dyscrasias or purpuras may show bleeding from the gastric mucous membrane. Massive hemorrhage in an ulcer case usually results from injury to the wall of a small blood vessel, and it has been pointed out that if the vessel has been cut across transversely, retraction of the bleeding stump is facilitated and hemorrhage is only transient, whereas if the injury has resulted only in the sloughing out of a side of the vessel, retraction is very difficult and prolonged bleeding is the rule. In old, indurated ulcers, usually caused by perforation or partial perforation with resultant excessive reaction in and around the ulcer area, exhibiting a horny infiltration with perigastric or periduodenal adhesions, a bleeding vessel may be held stiffly open, unable to retract. This generally results in continuous and profuse hemorrhage until the patient is exsanguinated. Even on the operating table such bleeding cannot be stopped without extensive resection, fatal to the patient. Fortunately this type of case is rare and in our experience hemorrhage has usually occurred in new and often rather small ulcers, which heal rapidly, so that in a series of one hundred and twenty cases studied by fractional gastric analysis and thorough Roentgen examination within sixteen or eighteen days of the onset of bleeding, we found no evidences of ulcer in fifteen cases (see Table I). In our series of cases the age varied from sixteen to eighty-two years, but the average was forty-two years, which is in agreement with statistics by other authors. The males (88) also

predominated over the females (32). There were only three colored patients in the series.

SYMPTOMS

Massive hemorrhage is, of course, manifested by the vomiting of a considerable amount (8 ounces or more) of fresh blood, by the passage of large tarry stools, or both. It would be expected that hematemesis would always be accompanied by melena, and in our

TABLE I
Gastric hemorrhage

120 Cases—Findings	
Duodenal Ulcer	78—60%
Gastric Ulcer	16—13%
Gastric and Duodenal	4—3%
Marginal or Jejunal	4—3%
No Ulcer Found	15—12%
Pyloric Stenosis	6—5%

series of one hundred and twenty cases (see Table II), 67% showed this combination. Twelve patients failed to show gross blood in the stools, having undoubtedly vomited most of the blood which had spilled. Only 23% of our cases showed melena alone—patients do not consider this as serious as hematemesis and do not come to the hospital unless in very bad condition. A history of previous ulcer symptoms was obtained in 86% of our patients. Hemorrhage occurred as a first symptom in but seventeen patients or 14%, all the others having experienced more or less pain preceding the onset of bleeding. A history of previous massive hemorrhage was obtained in 39% of our cases, of whom eleven or 9% had had two or more previous hemorrhages. Usually these previous hemorrhages had been recognized as such by the patients, but occasionally only a history of an attack of fainting and dizziness, accompanied or followed by vomiting, the nature of the vomitus not having been noted, or by "diarrhea," with no observation of the stools. Succeeding

TABLE II
Gastric hemorrhage

120 Cases—Symptomatology	
Hematemesis (alone)	12—10%
Melena	28—23%
Both	80—67%
Previous Ulcer	104—86%
Previous Hemorrhage	47—39%
Previous Operations	4—3%
Hemorrhage first symptom	17—14%

pallor, weakness, thirst and general malaise had often been attributed, even by their physician, to "ptomaine poisoning" or a "heart attack."

EXAMINATION

When first seen, the patient who has had a massive hemorrhage is in shock, appears frightened and apprehensive, is chilly and complains of great thirst. Marked pallor, a rapid, weak pulse, low blood pressure and cold extremities demand immediate attention. Although the need is for absolute rest, making it unwise to dis-

turb the patient by too complete and thorough general physical examination, it is nevertheless desirable to determine as accurately as possible, by questioning and observation, whether the bleeding has originated in the mouth, nose, throat or pulmonary tree, whether hepatic enlargement or gross abdominal tumors are present or whether there is evidence of a perforation accompanying the hemorrhage. While complete physical examination should be deferred until cessation of the hemorrhage, certain laboratory tests should be carried out immediately.

Blood counts, performed daily for three days, and then every two or three days, may show normal findings the first day, before blood volume has been replaced by absorption from the tissues. During the next twenty-four or forty-eight hours there is a steady fall in the count, even though all bleeding may have stopped, and after two or three days more a steady rise occurs. Table III shows the lowest points to which the red blood cells and hemoglobin fell, the average for our series of one hundred and twenty cases being 2,800,000 and 57% respectively, the lowest 1,100,000 and 14%. The white blood cells showed but slight variations from the normal. A distinctly increased

TABLE III
Gastric hemorrhage

120 Cases—Laboratory Findings			
	Lowest	Average	
Hemoglobin	14%	57%	
R. b. c.	1,100,000	2,800,000	
Average Gain	20%	1,700,000	
Urea N Highest 70 Average 32			
<i>Gastric analyses</i>			
	Highest	Lowest	Average
Free HCl	110	0	55
Total Acidity	140	10	75

leucocyte count should therefore be regarded with great suspicion that a perforation or other complication may be present. The same would be true of a marked rise in the percentage of polymorphonuclear leucocytes, which is usually normal or very slightly increased, with an occasional patient showing an actual leucopenia. Blood chemistry findings were interesting in that our cases showed a blood urea nitrogen averaging 32 mg. per 100 cc. with a high point at 70 mg. Usually the findings returned to normal within a few days or a week. Failure to do so was often an indication that bleeding was continuing, as pointed out by Ingegno four years ago, in a report emanating from our service at the Long Island College Hospital. Blood coagulation tests—coagulation and bleeding time, platelet count and prothrombin estimation—showed increase in all factors, except in the rare cases of blood dyscrasia. In view of this finding we long ago realized the uselessness of routine treatment by coagulants.

Fractional gastric analysis (Table III) was not done in our cases until nearly two weeks after the hemorrhage. At this time a fractional analysis after intramuscular injection of histamine disclosed that the usual secretory curve was one indicating a reflex, con-

tinued secretion, with the highest free HCl 110 and Total Acidity 140 and the average free HCl 55 and Total Acidity 75. In less than one-half of our cases was any visible blood found in the contents, indicating that rapid healing had taken place. Overnight retention was, of course, found in the stenosis cases.

Roentgen examinations were begun a day or two after the gastric analysis, unless this showed considerable bleeding still to be present. The average day for the beginning of the gastro-intestinal series was the sixteenth. During this period there had been an opportunity for the smaller ulcers to heal so that in our one hundred and twenty cases (see Table I) 12% showed no lesion. Of the others 13% showed definite gastric ulcer and 60% duodenal ulcer, and 3% showed both. Marginal or gastrojejunal ulcer was found in 3%. Pyloric stenosis was found in 5%. In all possible instances the patients were followed until Roentgen evidence of complete healing had been obtained or after operation had been performed.

PHYSIOLOGY

A consideration of the physiological principles to be considered following a massive gastric hemorrhage is of great help in developing a satisfactory course of treatment. When a large hemorrhage occurs from any cause, the immediate reaction is shock, as evidenced by dizziness and faintness, due to cerebral anemia and anoxemia, a definite lowering of blood pressure, and a compensatory increase in pulse rate. The patient may actually lose consciousness or may be merely so dizzy as to be compelled to lie down, the recumbent posture making it easier to maintain circulation. The lowered blood pressure and diminished blood volume result in a decrease in the force and volume of flow through the injured blood-vessel, facilitating the formation of a clot and thus stopping the hemorrhage. Meanwhile all coagulation factors are being mobilized, prothrombin is increased in amount, platelets multiply and at the site of bleeding there is an accumulation of factors concerned in healing and the combating of infection—lymphocytes, reticuloocytes, round cells, etc. The very gradual replacement of blood volume by absorption of water from the tissues permits the formation of a firm clot and its organization. The stomach usually becomes filled or partly filled with blood, even though some may be vomited. The filled stomach shows ordinary slow peristalsis and the blood combines readily with hydrochloric acid and pepsin, thus preventing these from attacking the edges of the bleeding vessel or the thrombus forming within. So far, nothing has occurred to interfere with prompt and complete control of the bleeding. Soon the stomach empties itself, the much-stimulated and powerful gastric secretion is left free to attack vessel and thrombus, and hunger contractions, intermittent, and increasing in force, tend to cause sudden and drastic changes in the pressure behind the thrombus, making it liable to be blown out. Fortunately, however, the patient is thirsty and hungry, and if he takes food in moderation and not enough fluid internally to increase blood volume materially, hunger contractions are stopped and gastric secretions again become fixed with the food. The general weakness due to the hemorrhage induces the patient to stay in bed, thus tending to maintain the low blood pressure so desirable during the period of organization of the thrombus. Thus, if nothing is done to the patient, if he is allowed to follow his own

impulses and if there is nothing present at the site of bleeding to interfere with the retraction of the bleeding vessel and formation of a thrombus (see discussion of pathology, above), everything tends to promote such clotting, and the patient recovers more or less rapidly from the results of the hemorrhage.

On the other hand, if the patient is treated according to the older standard methods, let us see what happens. Starvation for a few days (as also aspiration of all stomach contents) results in intermittent periods of intense hunger contractions, alternately increasing and decreasing the irritation and pressure at the bleeding point, and tends to loosen the clot during this period before it has become firmly organized and adherent to its vessel wall. Also, the gastric juice, with no stomach contents to attack, may dissolve out the clot or actually attack the vessel wall, which is not protected from digestion as is the mucosa. Besides this, starvation increases the patient's restlessness and lowers his resistance. Sudden increase in blood volume and pressure, induced by transfusion or parenteral

TABLE IV
Gastric hemorrhage

Mortality—Older Methods			
Author	Cases	Deaths	Per Cent
Bulmer	467	48	10.7
Goldman	319	39	11.1
Christianson	280	23	7.9
Aitken	231	20	8.5
Chesman	191	45	25
Jankelson	180	18	9
Burger & Hart	117	21	18
Crohn	94	4	4.2
Lynch	52	10	19
Huntton	41	6	13
Pfeiffer	40	3	7.5
Total	2,066	240	11.6

administration of other fluids, will tend to blow out the clot, and three of the deaths in our patients seemed to be attributable to this cause, transfusions or infusions having been given before the patients came under our care. The use of coagulants locally or parenterally, while doing no harm, is practically never required, all coagulation factors being naturally increased in potency. The use of ice externally is contrary to the generally accepted dictum that warmth is necessary in shock, and besides makes the patient miserable and cold, and ice internally can have no effect except to increase the circulation in the gastric wall, an undesirable result. Lavage, whether with water, astringents or other agents may conceivably tend to increase bleeding. Operation as a routine procedure is unnecessary, and in the cases showing the bleeding vessel held in a mass of horny scar tissue and surrounded by adhesions due to perforation or deep penetration, may present such mechanical difficulties that the operative mortality is excessive. The mortality from the older routine treatment, without operation, in 2,066 cases, gathered from literature here and abroad and shown in Table IV varied from 4.2%

TABLE V
Gastric hemorrhage

Mortality Operated Cases

Author	Cases	Deaths	Per Cent
McCluer	22	5	22.7
Aitken	21	7	33.3
Burger & Hart	20	5	25.0
Januelson	11	3	27.0
D'Abreu	10	3	30
Hinton	8	4	50
Total	92	27	29.3
Early operations (within 48 hours)			
Finsterer	16	2	4.3
Gordon Taylor	22	2	9
Total	68	4	5.8

to 25%, with an average of 11.6%. The general operative mortality (Table V) was 29.3%, but as in most instances these operations had been done later, after it had been found that bleeding was showing no tendency to stop spontaneously, we are comparing this mortality with that where operation had been performed within the first forty-eight hours when it was only 5.8%.

TREATMENT

The treatment recommended by me originally, based upon physiological considerations and resulting in a mortality of only 2.3% in a series of one hundred and seventy-three cases treated by D'Albora and myself (Table VI) has been changed in its minor details, but the principles involved have remained the same. Meulengraecht, whose treatment is along similar lines, has had a slightly lower mortality, but I believe that as the mortality really depends on causes which are irremediable, it will be found to remain in the neighborhood of 2% in long series of cases. Thus an analysis of the reason for our six deaths (Table VII) shows that while three died soon after large transfusions and therefore were not really treated by our method, the other three, all submitted to autopsy, showed the type of complication which would cause persistent

TABLE VI
Gastric hemorrhage

Mortality—Newer Treatments

Author	Cases	Deaths	Per Cent
Meulengraecht Method:			
Meulengraecht	285	3	1
Vendt	288	7	2.4
Total	574	10	1.7
Author's Method:			
D'Albora	53	1	1.8
Andrewsen	120	3	2.5
Total	173	4	2.3

bleeding which could not be controlled except by too-extensive surgical procedures.

Based upon physiological indications previously discussed, the treatment we recommend is as follows:

Shock should be treated by absolute rest in bed. Occasionally in a restless patient, morphine hypodermatically is required during the first twenty-four hours, but psychological treatment usually suffices to allay apprehension and stimulate cooperation. Explaining that the condition is not serious, that rest will encourage clotting and prevent continuing hemorrhage and that the restricted diet is necessary to stop the bleeding, we find our patients soon lying quietly in bed, often reading the paper or listening to the radio. A few hot water bags help to maintain body heat and make the patient comfortable, but over heating should be avoided, as this is distressing and weakening. I know that many patients have been so badly frightened by the hustle and bustle attending the measures resorted to under the old methods of treatment that it would be weeks before morale was restored. With attendants calm and encouraging, with no screening-off of the bed, with, if possible, a convalescent hemorrhage case in the next bed to encourage him, the patient, except for his pallor, ap-

TABLE VII
Gastric hemorrhage

120 Cases—Mortality

6 Deaths:

1. Exsanguinated—transfusion—died 24 hours.
2. Large transfusion.
3. Transfusion plus glucose.
4. Autopsy: gastric—old perforation, horny induration.
5. Autopsy: duodenal—old perforation, horny induration.
6. Autopsy: pyloric stenosis—prepyloric ulcer.

3 Deaths after transfusion, not counted.

Corrected mortality—3 cases—2.5%.

pears no different from other uncomplicated ulcer patients in the ward.

The bleeding area is treated by local applications of food. I have pointed out the desirability of controlling the undesirable and actually harmful hunger contractions and of preventing digestion of clot and injured vessel wall, by keeping food in the stomach. If the food, in addition to being soothing, combining readily with hydrochloric acid and not overtumulating its production, also has the effect of encouraging blood coagulation, we have an ideal combination. Gelatin has long been known as an excellent coagulant, whether locally applied or parenterally administered, and it is readily combined in a soothing liquid food mixture. Formerly our gelatin solution was made with water, and contained sugar and fruit juice to give it nutritive value (see Table VIII). After two days of these feedings, high calorie gruel and milk mixtures were substituted for every other gelatin feeding. In recent years the gelatin has been combined with milk, cream and glucose, and flavored with coffee, tea, chocolate or vanilla, making a drink enjoyed by nearly all patients and found to be even more efficient than the aqueous mixture. The patients are given at least 1800 calories during the first day after the hemorrhage, feel better

TABLE VIII
Gastric hemorrhage

Feedings Immediately After Hemorrhage					
Gelatin-Milk Mixture:					
	Amt.	Carb.	Prot.	Fat	Cal.
Gelatin	30 gm.		27		100
Dextrose	60 gm.	60			240
Cream (20%)	100 cc.	3	3	18	180
Milk	900 cc.	36	27	27	550
Totals		99 gm.	57 gm.	45 gm.	1000 Approximately

Formula to be made fresh every 12 hours, kept cool, but not in refrigerator, to prevent jelling.
Given cool or warm. Plain or flavored.

First 4 days: 6 oz. every 2 hours.

5th and 6th days: add 2 of above feedings one of any of following foods:

1 egg—soft boiled, poached or raw

cereal—3 oz.

eustard, jello or ice cream.

7th and 8th days: add 2 of above foods to each of 3 feedings.

9th day: Ulcer diet.

NOTE: At times the patient cannot tolerate the thick milk-gelatin mixture. In such cases use the gelatin-water formula, as follows:

Gelatin-Water Mixture:

	Amt.	Carb.	Prot.	Fat	Cal.
Gelatin	30 gm.		27		100
Dextrose	90 gm.	90			360
Juice of 2 oranges		20			80
Water	1,000 cc.				
Totals		110 gm.	27 gm.		540

and are in a better condition to promote healing of the lesion. In patients allergic to milk or who do not take the formula easily the old gelatin-water solution is still used. The routine as to quantities prescribed is shown in Table VIII, and Table IX shows the routine ulcer diet which I have used for years and which, in hemorrhage cases is gradually added to after a month or six weeks. Although repeated tests on our patients' blood and urines have shown no diminution in the cevitic acid content, we have in recent years added vitamin concentrates to our diets.

Anemia does not as a rule require special treatment, the rapid, spontaneous rise in blood counts having already been mentioned. However, repeated blood counts are done, blood chemistry determinations are made, blood coagulation tests are performed and blood pressure records are kept, so that any evidence of continued bleeding may be promptly observed and treatment instituted. The patient's blood is typed on admission and prospective donors are cross-matched, so that, if the patient shows a severe anoxemia, as evidenced by air hunger or a weak, thready pulse, small transfusions can be promptly given. Usually 150 to 200 cc. of blood is sufficient—more is undesirable. Although in our series of cases, small transfusions were given in the first ten days to seventeen patients, constituting 14% of the total number, in recent years the percentage has been less than 5%, as we have realized that even what appears like very serious bleeding will usually cease spontaneously if no extra fluid is suddenly added to the circulation. Iron, by

mouth or intramuscularly, may be given, but our statistics show that it has no particular advantage. Coagulants are very rarely required.

Constipation is encouraged—that is, nothing is done to disturb intestinal motility during the early days succeeding the hemorrhage. Mineral oil, one-half ounce per day, may be given after the second day, and, if required, oil retention enemas are administered after four or five days and thereafter as indicated. No other measures are ever used to produce defecation. All stools are examined for occult blood.

Operation for hemorrhage is a serious matter. While statistics, quoted above, have shown that operation performed as a routine in the first forty-eight hours after the onset of hemorrhage showed a mortality rate of less than 6% in the hands of two expert surgeons, yet, when we realize that only two or three per cent die when not operated upon, the risk of early operation would appear unjustifiable. When continued bleeding is present and exsanguination is imminent, resort to operation is attended by a very high mortality and surgeons are loth to operate. Surgery was refused in the cases in our series which died, because it was realized that the patient could not survive the double shock of hemorrhage and operation. Where operation is performed, extensive procedures, such as resection, are usually necessary, as pointed out previously in this article. The hemorrhage reported to have been stopped by simple gastro-enterostomy would undoubtedly have ceased spontaneously except where pyloric stenosis was definitely the factor which kept the bleeding vessel from retracting. Later operations for such complications as stenosis or walled-off perfo-

TABLE IX
Gastric hemorrhage

Ulcer Diet

Breakfast:

Milk 8 oz., with cream if desired.

Cereal 5 oz., with milk or cream.

Egg—1 soft boiled or poached.

Bread or toast with butter, 1 or 2 slices.

Fruit juice or stewed fruit (at end of meal).

Mid-morning:

Milk—8 oz., cream $\frac{1}{2}$ oz., dextrose $\frac{1}{2}$ oz., with cocoa if desired.

Always with crackers, toast, bread or cake.

Luncheon:

Milk 8 oz.

Baked or mashed potato or plain spaghetti.

Egg—1 soft boiled or poached, or cream cheese.

Bread and butter, 1 or 2 slices.

Pudding, eustard, gelatin, ice cream, or stewed fruits.

Mid-afternoon:

Same as mid-morning.

Supper:

Same as breakfast or luncheon.

At bedtime and during night every 2½ hours, if awake—same as at mid-morning.

Olive oil—½ oz. three times a day before meals.

Mineral oil—½ oz. at bedtime.

Water: ad lib.

Salt: Not restricted.

Vitamins: As required.

ration with resulting deformities should be performed as indicated.

After-care. Two weeks after admission, when repeated stool examinations show absence of blood or only small amounts of occult blood, a fractional gastric analysis is done, and if no visible blood is present, Roentgen examination is begun the next day, thus giving early information as to the source of the

TABLE X
Gastric hemorrhage

120 Cases—Treatment	
Transfusion 1 to 10 days	17—14%
After 10 days	25—20%
Operations for Hemorrhage	None
For Pyloric Stenosis	5 (later)

hemorrhage and pointing out the indications for further treatment. Then focal infections are searched for and eradicated, such operations being preceded by transfusions if indicated. About 20% of our patients were thus given blood after the first ten days in the hospital (Table X). The patients can usually be allowed to go home within four or five weeks, to be followed afterwards in clinic or office.

SUMMARY

In summarizing, I shall present the following outline of the indications for treatment and the routine procedure in hemorrhage cases, taken from the Ward Manual of the Medical Service at the Long Island College Hospital.

INDICATIONS FOR TREATMENT

Condition	Treatment
Shock	Rest, warmth, morphine
Apprehension	Quiet, psychic treatment
Local Bleeding	Soothing, coagulant, ant-acid diet
Hunger Contractions	Frequent, nutritious feedings
Severe Anoxemia	Very small transfusions
Anemia	None or later iron and transfusions
Impaired Coagulability	Coagulants, blood, vitamins
Constipation	Mineral oil and oil enemata (4th day).

ROUTINE IN GASTRIC HEMORRHAGE CASES

1. Treat Shock by rest, warmth and morphine (latter only if required).

2. Quiet Apprehension, do not awaken. Keep bed in quiet location.

3. Treat Bleeding Area: Order Gastric Hemorrhage Diet and nothing else by mouth.

4. Type and match blood for transfusion. No transfusion in first ten days except for air hunger or very weak pulse. Then only 180 to 200 cc.

5. Special charting for blood pressure and feedings.

6. Blood count every 2 days. Marked anemia may require transfusion after ten days and iron after meals.

7. Blood Coagulation tests. Coagulation and bleeding time, platelet count, prothrombin—repetition and treatment as indicated.

8. Blood Chemistry (Urea Nitrogen particularly) on admission and at two day intervals until normal.

9. Test all stools for occult blood until this disappears.

10. If no defecation: Mineral oil, $\frac{1}{2}$ ounce each night, beginning second night. Retention oil enema on fourth day and each night thereafter, if required.

TO BE AVOIDED

1. Ice: Externally, increases shock. Internally, stimulates gastric circulation.

2. Parenteral fluids: Increase blood volume and pressure—cause more bleeding. N. B. Small transfusions may be required in severe anoxemia. See Routine.

3. Stimulants (digitalis, adrenalin, etc.): Tend to increase bleeding. Only used in dire emergency.

4. Alkalies: Stimulate secretion. Irritate bleeding area.

5. Excitement or Worry: Increase shock and reaction may increase bleeding.

6. Examinations, manipulations or treatments, except as absolutely necessary, especially in first few days.

In closing I wish to thank my associate, Dr. S. C. Franco, for his valuable aid in gathering the statistics presented, to Dr. J. C. LaDue, a former interne, who permitted me to incorporate statistics he obtained from our hospital records, and which he will shortly present at the American Medical Association meeting in St. Louis, and to Dr. S. B. Thomas of Brooklyn, for permission to use operative statistics from a paper he read but did not publish.

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Gastro-Intestinal Hemorrhage From Otherwise Symptomless Lesions, With Special Reference to Duodenal Ulcer*

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HEMATEMESIS or melena, or both, are reliable evidence of gross hemorrhage from the upper portion of the gastro-intestinal tract, which may be due to a variety of causes. When such hemorrhage is associated with a history of upper abdominal pain or discomfort related to the digestive cycle and with other digestive disturbances, one logically assumes the presence of some type of intrinsic lesion of the stomach or duodenum until proved otherwise. Every now and then one sees patients whose sole complaint is the vomiting of blood and the passing of tarry stools, singly or repeatedly, and of varying degrees of severity. Such patients have never experienced pain, discomfort or indigestion. What are the circumstances that give rise to such a state of affairs, and to what extent do gastro-duodenal lesions, so-called silent, concealed or asymptomatic lesions, play a role?

DUODENAL ULCER AND DUODENITIS

For a number of years we have been cognizant of the fact that hemorrhage may be the sole manifestation of chronic duodenal ulcer, or of chronic duodenitis. As the former is the commonest gross lesion of the upper portion of the digestive tract encountered in American medical practice, such a manifestation is of great clinical import and interest.

The incidence of hemorrhage associated with otherwise asymptomatic duodenal ulcer or duodenitis was determined on the basis of a study of 1039 verified cases. In seventeen cases, or 1.5 per cent, hemorrhage was the sole sign of the lesion. In another twenty-four cases, or 2.2 per cent, in addition to hemorrhage, a history of vague or mild digestive disturbances elicited only on repeated questioning, was recorded. Thus, in a total of 3.7 per cent of the cases, painless hemorrhage constituted the outstanding, almost exclusive, manifestation of the ulcer. Considering the fact that only 20 per cent of duodenal ulcers give rise to gross hemorrhage, these figures are of interest because they indicate that hemorrhage is a painless, almost exclusive feature in 18.5 per cent of the cases of bleeding ulcers. There was another group of fifteen cases in which hemorrhage was the initial sign, and in which, after an otherwise symptomless period of variable duration of months to years, the characteristic pain and digestive disturbances eventually made their appearance.

It is obvious that hematemesis or melena, or both, can be the sole expression of a duodenal ulcer or its equivalent. It follows that if hematemesis or melena

can be the sole expression of an ulcer of the duodenum, it also can be that of any ulceration of the digestive tract, acute, subacute or chronic, situated anywhere between the lower half of the esophagus and the lower portion of the ileum. Even such a rare lesion as a diverticulum of the stomach may manifest itself in this way in view of the reports of Sutherland (1), and Brown and Priestley (2). The frequency with which painless hemorrhage occurs in cases of chronic gastric ulcer on the basis of our own material as yet has not been determined. Cases 1 and 2 are illustrative of chronic duodenal ulcer and chronic duodenitis, respectively.

Case 1. A woman, forty-nine years of age, registered at The Mayo Clinic February 1, 1938. In 1932, without provocation, she had experienced a sudden attack of nausea, profuse hematemesis, shock and syncope and thereafter passed tarry stools for a period of ten days. She had experienced a similar attack in 1936. Again, on January 15, 1938, she had noticed tarry stools and weakness for five days. At no time did she experience any epigastric pain or indigestion. The results of physical examination were essentially negative. The patient was of nervous temperament and hypersensitive. Gastric intubation was not done because of the recent hemorrhage. Roentgenologic examination of the stomach and duodenum disclosed deformity of the duodenal cap characteristic of chronic duodenal ulcer. In the absence of pain and other complications, medical treatment was recommended. The patient had enjoyed good health up to the time of our last report from her in March, 1939.

Case 2. A man, twenty years of age, registered at The Mayo Clinic, March 9, 1937. At irregular intervals since February, 1931, he had experienced attacks of melena, twice associated with moderate hematemesis, which in turn caused anemia and prostration. His most severe attack occurred in October, 1936. Intense social activities, such as fraternity "rushing" parties, provoked bleeding. He had never experienced pain or indigestion. Analysis of the gastric contents revealed 64 clinical units of free hydrochloric acid. Roentgenologic examination of the stomach and duodenum disclosed bulbar irregularity and irritability characteristic of duodenitis. Medical treatment was carried out. The patient was enjoying good health in March, 1939, when he was heard from last.

Of importance equal to, if not greater than, gastric or duodenal ulcer and gastric carcinoma as the cause of painless hemorrhage is chronic gastritis, benign tumor of the stomach, splenic anemia, biliary cirrhosis and certain late postoperative sequelae. Of less importance because of their comparative infrequency, yet of great clinical interest, are para-esophageal hernia, ulcer and neoplasms of the small bowel and of Meckel's diverticulum. There remains an indeterminate group in which it is impossible to ascertain defi-

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nately the cause of gastro-enteric hemorrhages, especially in the earlier stages of the process, owing to the complete absence of any objective data. As a matter of fact, in a considerable percentage of such cases, the cause of the hemorrhage may remain undetermined even after exploratory operation. In this group are not intended to be included those instances of silent solitary hemorrhage in which there has not been antecedent or subsequent developments.

CHRONIC GASTRITIS

The latent subclinical or asymptomatic nature of gastritis in its various forms has been substantiated by numerous observers on the basis of pathologic and gastroscopic observations. This fact, in addition to the high incidence of the disease as reported by competent gastroscopists, both in America and abroad, justifies the conclusion that chronic superficial and hypertrophic gastritis, if not the most frequent, is one of the most frequent causes of painless hematemesis and melena. Former statistical data relative to the various causes of gastro-enteric hemorrhage are of doubtful scientific value because, almost without exception gastritis as a factor has not been taken into consideration. The present tendency in many clinics and hospitals to carry out routine gastroscopic examination in all unexplained cases of gross hemorrhage has been a revelation in many ways but especially in the elucidation of the important role that superficial inflammatory mucosal lesions play in gross bleeding from the upper portion of the digestive tract. Recent gastroscopic examinations have demonstrated the fact that chronic duodenal ulcer is frequently accompanied by such superficial inflammatory lesions, as well as by simple erosion and submucosal hemorrhages and that the source of the bleeding usually attributed to the ulcer, on the contrary, is often found to be due to the superficial inflammatory lesions, simple erosion or submucosal hemorrhages.

Case 3. A man, thirty-two years of age, registered at The Mayo Clinic January 9, 1939. In 1932 and in 1937 he had experienced unexplained seizures of sudden weakness. In retrospect, this may have been due to melena, as the condition and color of the stools were not observed at that time. In February, 1938, the patient had experienced a similar attack, with vomiting of coffee-ground material. At that time, he had observed tarry stools. Again, in December, 1938, he had had an attack of melena and prostration, and three days later, hematemesis and melena, resulting in shock. The concentration of hemoglobin was 44 per cent. He had not experienced epigastric pain or indigestion at any time. Repeated roentgenologic examinations of the stomach and duodenum gave negative results. Gastroscopic examination disclosed a definite hypertrophic gastritis of the fundus. The tonsils were definitely infected and were removed in the hope that this infection was the source of the patient's difficulty.

BENIGN TUMOR

A paucity of symptoms and a great tendency toward bleeding is characteristic of the majority of benign tumors of the stomach. On that account this possibility should be excluded in every case of painless hemorrhage, or of obscure anemia that results from long continued occult bleeding. These lesions are not as infrequent as previously was supposed. Already 176 surgically verified cases of benign gastric tumor have come under our observation, exclusive of those found

at necropsy when death was due to other causes. Improved roentgenologic technique has made possible roentgenoscopic detection of the majority of these tumors, even the smaller adenomatous polyps. However, polypoid forms of hypertrophic gastritis, which have much in common with polypoid gastric tumors, usually are recognizable only on gastroscopic examination.

SPLENIC ANEMIA AND HEPATIC CIRRHOSIS

Painless, severe and recurrent hemorrhage and the symptoms engendered by severe anemia may be the sole complaints of a patient who has splenic or hepatic disease, or both. That some members of the profession are quick to jump to the conclusion that a hemorrhage is the result of a gastro-duodenal ulcer, even in the absence of symptoms of pain or indigestion, is sometimes exemplified by the fact that an enlarged spleen remains undiscovered until late in the course of the disease. Under the circumstances there should be little difficulty in making a proper diagnosis. In cases of hepatic cirrhosis without obvious increase or decrease in the size of the liver and without frank signs of portal hypertension or icterus, considerable difficulty may be encountered, especially in the early stages. In doubtful cases, tests of hepatic function, roentgenographic examination of the lower portion of the esophagus for varices, or laparotomy, are usually necessary in order to establish the diagnosis. Cases 4 and 5 are illustrative of this group. Comparatively, such lesions fortunately are infrequent causes of hemorrhage. Rivers and Wilbur (3), in a review of cases of hematemesis encountered in the clinic over a period of two years, found that only in about 9 per cent of the cases was hemorrhage diagnosed as being due to causes extraneous to the gastro-intestinal tract; such were principally due to various forms of blood dyscrasia, splenic disease and hepatic cirrhosis.

Case 4. A man, twenty-five years of age, registered at the clinic January 10, 1938, because of "repeated hemorrhages from the stomach and bowels." In 1934, four years previously, he had experienced his first hemorrhage. This was characterized by severe hematemesis on two successive days, followed by the passage of tarry stools for six days. Although he had not experienced abdominal pain or indigestion prior to, during, or since these hemorrhages, he was treated at that time for gastric ulcer. Six months later he had noticed tarry stools for four days. Then, for a period of two years, he remained entirely free of hemorrhages. In September, 1936, he had two massive hemorrhages, chiefly hematemesis, which resulted in syncope and shock, and repeated transfusions were necessary. In December, 1937, he had experienced melena for several days, which had been preceded by weakness, and by tachycardia on exertion. There were no symptoms or signs suggestive of hemophilia, purpura hemorrhagica, or other dyscrasias.

Physical examination showed that the spleen was enlarged. The patient had been totally unaware of this. The spleen extended for four fingerbreadths below the left costal margin. The concentration of hemoglobin was 62 per cent; erythrocytes numbered 3,510,000 and leukocytes, 5400, per cubic millimeter of blood. Differential count and morphologic examination of a blood smear did not reveal significant abnormalities. Roentgenoscopic examination of the stomach and duodenum gave essentially negative results, but varices were discovered in the lower half of the esophagus. Tests of hepatic function and estimation of serum bilirubin gave essentially normal results. The von den Bergh reaction was indirect. A diagnosis of splenic

nnemia with profuse hemorrhages from esophageal varices, was made.

A splenectomy, including ligation of the coronary vein and a Tnlma-Morison type of omentopexy, was done in January, 1938. This operation was preceded and followed by repeated transfusions of blood. The liver, gall bladder, stomach and duodenum were examined carefully at the time of the operation and were found to be normal. Since this operation the patient has enjoyed much better health than formerly, but he has had two mild hemorrhages after violent physical exertion, against which indiscretion he had been cautioned repeatedly.

Case 5. A man, thirty-two years of age, first entered the clinic January 7, 1935. In November, 1934, he had experienced a sensation of weakness and dizziness and soon thereafter had passed tarry stools, which recurred on three successive days. He stated that he "almost passed out." A month later he had a more severe hemorrhage, without syncope; it caused acute anemina and required two transfusions of blood. Otherwise, he had had no complaints of a gastro-intestinal nature. Except for evidence of moderate anemia, the physical examination gave essentially negative results. The concentration of hemoglobin was 70 per cent and erythrocytes numbered 3,860,000 per cubic millimeter of blood. The platelet count and the coagulation time of the venous blood were within normal limits. Other laboratory investigations, which included roentgenoscopic examination of the stomach and duodenum, tests of hepatic function, examination of the feces for blood when he was taking a meat-free diet, and examination of the esophagus for varices disclosed no abnormality. Cholecystographic examination, however, revealed a poorly functioning gall bladder. A similar result was obtained on examination several months prior to entering the clinic. Surgical exploration of the gall bladder, liver, pancreas and upper portion of the digestive tract was recommended but was refused.

The patient was re-examined at the clinic on June 21, 1935, because of melena of a week's duration which occurred two weeks previously. The roentgenologic findings were identical with those of the previous January.

The patient did not come under our observation again until after a lapse of four years. In the meantime, he had experienced about twelve more hemorrhages, seven of which were massive. Syncope was associated with three of them. He had been treated on the basis of a duodenal ulcer and alimentary allergy, but bleeding had occurred during active treatment for both conditions, on various occasions. Gastroscopy had been performed by a gastroscopist of international reputation on six different occasions up to very recently. The results of these examinations were essentially negative. Unusual physical and mental exertion, exposure to cold, and infections of the upper portions of the respiratory tract predisposed definitely to bleeding. Evidence of steatorrhea of progressive severity has been present for eighteen months. The spleen also was found to be enlarged recently. Examination at this time, at the clinic, disclosed esophageal varices, a high grade of retention of bromsulfalein, moderate splenic enlargement, an excess of fat in the feces, and a nonfunctioning gall bladder. Roentgenographic examination of the stomach and duodenum gave negative results. The serum bilirubin was within normal limits but the van den Bergh reaction was direct. A diagnosis was made of recurrent massive hemorrhage from esophageal varices incident to portal cirrhosis, and highly probable, associated chronic cholecystitis and chronic pancreatitis.

LATE POSTOPERATIVE SEQUELAE THAT GIVE RISE TO HEMORRHAGE

Hemorrhage that occurs several months or years after an operation for chronic ulcer, especially duodenal ulcer, constitutes one of the most perplexing diagnostic and therapeutic problems that the physician

encounters. Lesions that give rise to such hemorrhage are frequently otherwise symptomless by virtue of certain favorable conditions effected by the operation, or because the lesions are of a superficial character, confined to the mucosa, whether such lesions are localized or diffuse.

The diagnostic significance of late postoperative hemorrhage, whether silent or otherwise, is partly dependent on whether the original lesion was of the bleeding type or not. Hemorrhage that occurs after gastrojejunostomy for hemorrhagic duodenal ulcer usually implies that the bleeding had its source in the original lesion, as the result of reactivation, whatever the cause. Under such circumstances the hemorrhage is usually unassociated with any other symptoms, unless a jejunal ulcer also might have developed in the meantime. On the other hand, hemorrhage that occurs for the first time after gastrojejunostomy or after a Billroth II type of operation for a nonhemorrhagic duodenal ulcer, is usually indicative of the formation of a lesion, an ulcer or gastritis, at some site other than the original one. Case 6, while an unusual one, is illustrative of the latter type. Similarly, late hemorrhage that occurs after any operation in which the original ulcer was removed, implies the formation of a new ulcer, the presence originally of multiple ulcers, one or more of which was overlooked, or postoperative gastritis. As roentgenologic diagnosis of postoperative lesions which may give rise to hemorrhage is often very difficult, gastroscopic examination always should be carried out whenever there is any reasonable doubt about the diagnosis.

Case 6. A boy, seventeen years of age, first entered the clinic on January 9, 1928. He had had a gastrojejunostomy for congenital pyloric stenosis, elsewhere, in 1911, when only five weeks old. In May, 1926, fifteen years later, he had experienced a sudden collapse and anemia. In August, 1926, he had had massive hematemesis and melena, followed by syncope. At that time the concentration of hemoglobin was 25 per cent (Dare). Analysis of the gastric contents showed an absence of free hydrochloric acid, and roentgenographic examination of the stomach, the stomach and the duodenum did not reveal any abnormality. The diagnosis was late postoperative gastro-enteric hemorrhage of undetermined origin. On his return home, a local surgeon submitted the patient to operation, at which time he performed a Billroth II type of pylorotomy (January, 1928). The patient consulted us again on June 3, 1935, because of recurrent attacks of severe melena, which had been present periodically since 1930. Roentgenoscopic examination of the stomach and anastomotic region after resection showed nothing abnormal. However, operation was advised and on June 17, 1935, the operation was performed at the clinic and cystic polypoid hyperplasia of the mucosa of the stomach was found. The gastrojejunostomy was disconnected, the peri-anastomotic tissues were excised and an end-to-side anastomosis of the stomach and duodenum was done. The patient has enjoyed good health since the operation.

DIAPHRAGMATIC HERNIA

A number of observers, notably Gardner (4) and Boek and his associates (5), have pointed out that diaphragmatic hernia may be the cause of gross gastric hemorrhage or of secondary anemia of varying degrees of severity. One of our patients, who was eventually found to have such a hernia complained only of dyspnea and of edema of the lower extremities, which were the direct result of severe secondary anemia of which the patient was unaware. The bleed-

ing is usually attributed to venous congestion of the gastric mucosa caused by compression of the stomach by the diaphragmatic muscles. Harrington (6), who has repaired surgically many of these hernias, has been of the opinion that the bleeding has its origin in traumatic erosion or ulcer of the mucous membrane caused by the forceful pressure exerted during the attacks of vomiting, on the large, distorted and congested stomach, and by the trauma caused by the hernial ring as the stomach is forced in and out of this opening. This erosion may be superficial, or in cases of long standing, may become definitely ulcerated from repeated trauma. Reduction and repair of the hernia results in prompt healing of the traumatized mucous membrane and cessation of hemorrhages.

ULCER OR NEOPLASMS OF THE SMALL BOWEL

Ulcer or neoplasms of the small bowel, admittedly rare, or ulcer in a Meckel's diverticulum, may give rise to painless melena. In all obscure cases of hemorrhage, it is important to examine the small bowel roentgenologically even in the absence of pain or obstructive symptoms, if the investigations up to that time have failed to disclose any lesion in the stomach or duodenum. Recurrent melena of children or young adults, without gastric disturbances, always should raise the suspicion that a bleeding intestinal lesion is present, especially an ulcer of a Meckel's diverticulum. A history of hematemesis would exclude the presence of a lesion below the level of the duodenum or duodeno-jejunal angle. Case 7 is an example of a "silent" bleeding tumor of the small intestine.

CASE 7. A man, forty-three years of age, entered the clinic January 12, 1939. For three and a half years prior to this he had complained of almost daily belching and mild heart burn, the latter appearing soon after meals. In 1936, he had experienced an attack of nausea and prostration, followed by melena in forty-eight hours. The latter persisted for a period of eight days. Melena recurred in June, September and December, 1938. He had experienced vague gastro-intestinal disturbances, which were relieved by a bland diet and antacids. Roentgenologic examination disclosed a crescentic defect of the upper portion of the jejunum, characteristic of submucosal leiomyoma. There were also signs of ulceration of the central portion of the tumor. On February 4, 1939, a partial jejunectomy was done for a leiomyoma that measured 4 by 4 by 3 cm., with a region of ulceration of overlying mucosa 4 mm. in diameter. The patient had an uneventful convalescence.

UNDETERMINED CAUSES

A constant challenge and source of humility are those instances of gross hemorrhage coming under our purview from time to time in which it is impossible to determine satisfactorily the cause of the condition. In the presence of pain and other disturbances strongly suggestive of ulcer, gross hemorrhage would point strongly to organic disease, in all likelihood, an ulcer or gastritis, in spite of the absence of roentgenologic evidence of a lesion. Berkman (7), in a study of cases of concealed gastro-intestinal hemorrhage encountered in the clinic, has been of the opinion that the largest number of cases of unexplained hemorrhage is due to duodenal ulcer or regions of duodenitis. Of eighteen patients who had experienced hemorrhage of undetermined origin, who underwent exploratory operation in the clinic, Berk-

man (8) reported that the cause of the hemorrhage was determined in ten, seven had duodenal ulcers, one associated with gastric ulcer, one had a fibrosarcoma in a Meckel's diverticulum, one had an annular carcinoma of the upper part of the jejunum, and one had a questionably malignant lesion on the lesser curvature of the stomach. Infrequently, carcinoma of the ampulla of Vater is responsible for obscure instances of melena.

In the complete absence of pain or dyspeptic symptoms, superficial erosions, acute ulcers, focal or diffuse gastritis, or causes extraneous to the stomach or duodenum, as illustrated by cases 4 and 5, would play a probable role. It is reasonable to assume that gastroscopic examination, undertaken soon after a hemorrhage has occurred, might supply information that would be lacking later, owing to the evanescent nature of some of the superficial mucosal lesions which can give rise to hemorrhage. It would not be the better part of wisdom to urge surgical exploration in cases in which lesions are painless in order to establish a diagnosis, unless there was a reasonable threat of malignancy, or unless the hemorrhages were excessive and recurred at frequent intervals. Under any circumstance, it is essential that patients who suffer from bleeding of undeterminable cause be kept under observation, as developments of a tangible nature often take place sooner or later. It was pointed out early in this article that hemorrhage may be the initial sign of duodenal ulcer months or years before other characteristic subjective symptoms or objective signs appear.

Disorders of metabolism, toxicosis and avitaminosis, frequently difficult of recognition and appraisal, at times must be important etiologic factors in obscure instances of hemorrhage. In recent years various writers have ascribed to deficiency of Vitamin C a significant role, not only in cases of ulcer but especially in those of hemorrhagic ulcer. Numerous studies in nutrition have shown that in sub-clinical states, Vitamin D deficiency is very prevalent. Goldsmith and Ellinger (9), on the basis of their studies, have urged caution before attributing to ascorbic acid the role of an etiologic factor in any pathologic state. They are of the opinion that such depletion of the Vitamin C contained in the tissues may be only a concomitant finding or a result rather than a cause of the disease under consideration. Although vitamin deficiency may play an important role in capillary bleeding, I doubt that it has any importance in bleeding which is the result of arterial erosion.

Absence of pain in these cases of hemorrhage, from one cause or another, naturally raises the question of individual sensitivity. Determination of the degree of sensitiveness to pain by Lilman's (10) simple method was not done routinely in the cases under consideration, so that definite conclusions from this standpoint cannot be drawn. Crohn's (11) observations in cases of gastric and duodenal ulcer led him to believe that insensitive individuals may experience the most severe complications because such persons are deprived of one of the most important of nature's defense mechanisms, that is, the ability to feel and to react to visceral pain. In his group of cases of ulcer complicated by hemorrhage, 40.8 per cent were comparatively insensitive, in contrast to a normal of 12 per cent. To what extent we have been derelict in this respect is debatable, because the validity of Lilman's procedure

still awaits general acceptance and confirmation. Other factors bearing on individual sensitivity to visceral pain undoubtedly also play an important role, if not a dominant one, such as the nature of the underlying lesion, the depth of the lesion, the nature and degree of the resulting visceral dysfunction, and the extent of direct involvement of nerves or peritoneal structures. For example, one would not anticipate pain in cases of uncomplicated hepatic or splenic disease. Superficial lesions, such as those comprising the gastritides, frequently are painless. The paucity of symptoms in association with benign tumor can be attributed to the absence or paucity of gastric secretory, spastic and motor disturbances, as has been pointed out by Moore (12).

SUMMARY

Silent gastro-intestinal hemorrhage may be caused by various lesions that are intrinsic or extrinsic to the digestive tract. One of the commonest causes is chronic duodenal ulcer, or duodenitis. In 1.5 per cent of 1089 verified benign ulcerative or inflammatory duodenal lesions, hemorrhage was the sole sign. In another 2.2 per cent, or in a total of 3.7 per cent, painless hemorrhage constituted the outstanding, almost exclusive, manifestation of the disease. Painless hemorrhage may be the initial sign of a duodenal ulcer, occurring months or years before the usual symptoms are manifested.

Other lesions that frequently give rise to painless hemorrhage are chronic gastritis, benign gastric tumor, splenic anemia, hepatic cirrhosis, jejunal ulcer, gastrojejunitis and postoperative gastritis. Of less importance, because of their comparative infrequency, and yet, of great clinical interest as the cause of silent hemorrhage, are para-esophageal hernia, ulcers or neoplasms of the small intestine, and ulcer of Meckel's diverticulum.

For patients who are subject to recurrent hemorrhage from time to time, eventual developments may be such as to make possible a satisfactory diagnosis and the institution of the proper treatment. In some instances, the cause of the hemorrhage is not ascertained even after exploratory laparotomy. Whatever the cause, whether intrinsic or extrinsic to the digestive tract, unusual physical or mental stress or alcoholic indiscretions predispose to bleeding and should be guarded against by the patient.

Whether the absence of pain is due to individual nonsensitivity or to certain anatomic and physiologic factors, such as the depth of the lesion, the degree of resulting visceral dysfunction, the extent of direct involvement of nerves or peritoneal tissue, or to a combination of these factors, has not been definitely determined.

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DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore): I should like to discuss Dr. Andresen's paper.

There is no problem in therapeutics which will require more careful consideration nor cause greater anxiety to the clinician than the treatment of persistent or massive gastric hemorrhage. It may require the combined judgment and effort of both internist and surgeon to decide upon the best plan of treatment.

Prophylactically much can be accomplished. As soon as tar-colored stools are noted, the patient must be confined to bed under strict dietetic regulation, until bleeding ceases. Only by such precautions can massive hemorrhage sometimes be averted.

We are in accord with most of the conclusions arrived at by Dr. Andresen. Ever since Clement Jones presented his paper in 1921 before this Association, on his observations on hematemesis in which he called attention to the beneficial effects of gelatin in this condition, we have utilized gelatin mixtures in our clinic in the treatment of gastric hemorrhage with most satisfactory results.

On account of nausea and vomiting, this may be the only remedy that can be retained for the first day or two following the hemorrhage. Aside from the use of morphin and absolute rest, a soft diet is given for nine or ten days, and gradually enlarged to a regular and balanced diet in a manner much like that recommended by Dr. Andresen. Transfusions may be required at any time and the necessary grouping should be determined at the very beginning in order to be in readiness should the occasion arise.

In instances of massive hemorrhage with blood counts below two million and hemoglobin below 40 per cent, transfusions have been invaluable. We have found that small transfusions of 200 to 250 cc. of blood, repeated, if necessary, at intervals of three to five days, have been extremely helpful in stimulating blood formation as well as in controlling hemorrhage. When the stomach is distended with food remnants, fluids, or coagulated blood, lavage with warm water is a helpful procedure, but in our experience should not be resorted to unless considered absolutely essential.

We have not observed that the so-called coagulants have been of decided help in controlling the hemorrhage in any of our cases.

From our experience we are convinced that blood pressure readings play a far more important role in the prognosis of gastric hemorrhage than the low hemoglobin readings, although the latter often falls to the low value of 35 with subsequent complete recovery. A red cell count of two million or less is not unusual.

A fall in blood pressure to from 80 to 85 systolic without being followed by a rise, is always an alarming sign. A rise, however, is often indicative of a cessation of the bleeding. As soon as hemorrhage has been overcome, iron in the form of iron and ammonium citrate should be administered in large dosage, and it is now known that iron absorption is far better when alkalization is omitted.

As the result of this plan of treatment which in the main resembles that of Andresen and even Meulengracht, our mortality from gastric hemorrhage has been greatly reduced and the need of surgical intervention from this cause has fortunately become far less frequent.

We are certainly indebted to Dr. Andresen for his timely and most valuable paper.

DR. T. GRIER MILLER (Philadelphia): Mr. President and Members of the Association: I shall limit myself

largely to a discussion of Dr. Blackford's paper. He was good enough to send me a copy of it and, therefore, at some leisure I have been able to consider his and Dr. Cole's data on the mortality in hemorrhage from peptic ulcer. The data have been carefully analyzed, and their presentation should lead to clearer thinking about this very important subject, perhaps to a better selection of cases for surgery and eventually to a more satisfactory basis for the evaluation of various types of medical therapy.

Very properly Dr. Blackford has stated his criteria for the inclusion of cases in his group. I perhaps should point out that his exclusion of those patients who have anastomotic ulcer and of those who have moderate degrees of hemorrhage tends to increase his mortality. On the other hand, I wish to point out that he also excludes patients dying of post-operative complications after hemorrhage and that such exclusion tends to decrease his mortality rate. On that basis I question his right to solve his mortality for comparison with the data of most other authors.

As a matter of fact, comparisons of the data from various clinics on this subject is exceedingly difficult, if not impossible, not only because of differing objective criteria but also because of varying judgment as to the severity of the hemorrhage itself. Dr. Elsom and I, however, during last year carefully reviewed our own and others' data and have reported the results. We found that mortality after medical therapy ranged from zero to 25 per cent; the surgical mortality from 6 to 100 per cent. In all we obtained data on 6226 cases of grossly bleeding ulcer. Of those that had been treated medically, 8.7 per cent died; 28 per cent of those that had been treated surgically. Putting the two groups together, we found that 10 per cent of all the grossly bleeding ulcer cases had died. Dr. Blackford's total figure was only 11 per cent, which isn't very different, you see, from the average for all reported cases.

I was particularly interested in Dr. Blackford's references to the age incidence in the mortality from bleeding ulcer. As you noted from his chart, he had no patients die under forty-five. He had six die after forty-five. He is inclined to feel that the mortality is rather negligible under the age of forty-five; so does Dr. Crohn and so does Dr. Allen of Boston. Perhaps they are all right, but I should like to say that in our personal series of only sixty-eight cases we had a higher mortality in the patients under forty-five, namely, 14.6 per cent, as against 11 per cent in those patients who were more than forty-five years of age. The ages of our six cases under 45 years were 20, 28, 31, 39, 44 and 45.

I should also like to call attention to the fact that Dr. Blackford excluded three cases from his fifty-seven, two because they had post-operative complications, and one because an anastomotic ulcer was present; it happens that all those three were under forty-five years of age. So if we had included them, he would have had a 10 per cent mortality under forty-five. I wonder if he shouldn't at least have included those patients who died of post-operative complications. After all, weren't those patients operated on because they would otherwise have died, and did not the complications after operation develop because those patients' general condition was markedly impaired as a result of prolonged bleeding? If so, I think they should have been included.

I can't dispose so readily as Dr. Eusterman of the vital statistics data, but I should like to know about similar data from other public health departments.

DR. SIDNEY PORTIS (Chicago): I do not wish to prolong this discussion but I wish there were a rule of thumb by which we could handle all of these cases. The patient who intrigues me most is the one who has a massive hemorrhage associated with duodenal ulcer. This type of hemorrhage is very frequently associated with an eroded pancreaticoduodenal artery, and it should be suspected in a patient who has a known history of duodenal ulcer

and has a profuse massive exsanguinating hemorrhage. I think the sooner that these patients get to the operating table the more likely it will be that their lives will be saved.

I have seen enough of this evidence at the necropsy table to impress upon me the futility of medical treatment in trying to control this type of hemorrhage. The only treatment is immediate surgical intervention with adequate transfusions and to ligate the vessel.

The other point that occurred to me during the course of these papers was that in patients with bleeding duodenal ulcer, it is most important during the course of medical management, to keep the pylorus in a state of partial relaxation, and I think this can be accomplished by a sufficient amount of atropine, which will allay active peristalsis somewhat and tend to permit a more rapid healing of the bleeding ulcer.

DR. J. RUSSELL VERBRYCKE, Jr. (Washington, D. C.): Mr. President: My treatment of ulcer is very much like any politics. I am a hidebound conservative. I had an occasion to look over the records just before I left, and I have one slide I should like to have shown while I am making these several remarks.

I don't believe that the age incidence is as important as the diseases which naturally come with age; for instance, in looking over the mortality rate, I find that massive hemorrhage, not just gross hemorrhage, gave us a mortality rate of 3.1 per cent from ulcer, but when all massive hemorrhages were included, that is, cirrhosis, cancer, syphilis, we went to 11.9 per cent; in other words, our mortality rate from conditions which were not ulcer, is over three times that of ulcer cases.

I agree with the statement that the vital statistics are not very helpful, and I believe that many of the cases of hemorrhage reported as being due to ulcer without any studies having been made before the patient died, were probably not ulcer at all.

There are several statements that I want to make here. The first is about the time for operation, time for operation if the patient is seen not to be getting well under medical treatment. If that is true, the time for operation is after his respirations have ceased, because it doesn't make any difference if the patient gets practically pulseless. That is part of the reason for the hemorrhage stopping, and the main thing is not to get panicky, no matter how bad the patient gets, and not to rush from one thing to another.

The same thing can be said about transfusions. I say "never transfuse," that is, during the active treatment of the ulcer. Never add water. A patient may be dehydrated but don't pay any attention to that during the acute stage.

If anything has to be done, certainly small hypodermoclyses are better than anything else, but no transfusion and no intravenous of any kind.

Dr. Andresen doesn't like ice. I use ice and still stick to it. I can find fault with him—I don't like the iron in the stomach. I think probably one would irritate as much as the other, that is if either does harm. I would prefer to give my iron later on with hypodermics rather than introduce it into the stomach.

I noticed that our highest mortality came from post-operative marginal ulcers, from ulcer with cancer, cancer and syphilis, cancer with obstructions, plain cancer, cirrhosis, and Baile's.

DR. RALPH C. BROWN (Chicago): I should like to add my voice to the conservatism Dr. Verbruycke has just expressed and also note certain factors which I feel greatly influence the prognosis as well as the treatment of massive hemorrhage in peptic ulcer.

We are all influenced by the personal experience we have had when it comes to forming an opinion as to how likely a given patient is to die and what to do about it, and as I look back over the years I find that when faced with the emergency of a serious hemorrhage, I have

anxiety as to the outcome in only two groups of cases, namely, massive hemorrhage in the older individual who shows evidences of a marked degree of arteriosclerosis and the far larger group of cases in which the history of pain during the midnight hours indicates the presence of pyloric obstruction with continued gastric secretion or the continued night secretion which may accompany a large, chronic, deep-seated gastric ulcer.

With the massive hemorrhage patient lying before one the immediate objective is, of course, clot formation, but a blood clot is just as readily digested by gastric juice as egg albumen. The patient with no pyloric obstruction or continued secretion and with fairly good arteries may very well be left alone and nine times out of ten nothing further will happen to him. But no matter how effective the daytime management may be, if the forming blood clot is exposed to the digestive action of an excessive continued night secretion, the presence of which may be determined by aspirating with a Rehfuß tube, then hemorrhage is extremely likely to recur.

Therefore my plea is that we should keep in mind the necessity of recognizing, when possible, the existence of pyloric obstruction and continued secretion and of taking appropriate measures to safeguard the patient. The crux of the matter is effective acid neutralization, thus preventing digestion of the clot. Meulengracht achieves his low mortality figures by using frequent feedings and alkalis. If appropriate measures are also used during the night hours as well—and there are various ways in which a continued secretion may either be removed or neutralized—cessation of hemorrhage is likely to result. After forty-eight hours have passed without sign of recurring hemorrhage the patient will be relatively safe.

DR. RUDOLF SCHINDLER (Chicago): I was glad that Dr. Eusterman has pointed to the frequency of hemorrhage from painless ulcer. We have become aware of this fact especially since in the clinic of Dr. Palmer we examine our ulcer patients at very short intervals, intervals of two weeks or four weeks, gastroscopically as well as at X-ray. We see that the patient comes telling that he is feeling fine and we see a recurrence of his ulcer, and then, in quite a few cases it has occurred that some weeks later the first painless hemorrhage occurred.

I remember especially two cases of resected stomach in which the patient came back telling that he was feeling fine and gastroscopically I saw a very definite marginal ulcer in both cases, and both cases, two or three weeks later, had a gross hemorrhage, and in one of the patients a short time later I could see the thrombus in the midst of the ulcer and still the patient had no pain.

I observed three cases of myoma gastroscopically, and all three were referred because of gross gastric hemorrhage.

DR. JOHN L. KANTOR (New York): May I ask a question of Dr. Blackford? If every one of the operated patients in the older group died, why does he still recommend surgery in these older patients?

DR. FRANKLIN HOLLANDER (New York): Mr. President, I would like to introduce a very academic note into this discussion. For the last three years I have been sitting on the sidelines at our hospital and here at the meetings of the Association, listening to discussions on hemorrhage with a great deal of interest in this controversy.

Not being a medical man myself, I probably bring a little less bias to bear in my analysis of this problem than most of you clinicians do, and I have observed this very interesting thing: A discussion usually starts out with very well defined statistics. I think all three of the papers which we are discussing now are statistical. You present numbers as evidence of this or that or the other situation. Before the discussion has gone along very far, however, you are discussing your own clinical impressions on the situation. These clinical impressions arise in part from a

diffuse interpretation of what you observe at the bedside, a thing about which nobody can argue with you, and in part from a non-mathematical interpretation of the numbers which you put down on paper or on your lantern slides.

It seems to me that a great deal of your discussion would be simplified or made wholly unnecessary if you took your statistical data more seriously and consulted a biometrician about your fundamental facts before you attempted to organize your clinical ideas on these questions. I am fairly well convinced from my experience at our hospital in New York that a great many of the differences between groups of data with which you are dealing are statistically non-significant for various reasons; that you are arguing about differences which do not exist, and which appear in your studies only because of errors in what we call sampling. You pick a group of fifteen, or twenty five, or maybe even fifty cases in a particular situation. You get a certain numerical measure of your clinical result. If, in your own hospital or private practice, you were to pick a similar group of fifty, you might well find a markedly different result—even though your working conditions appeared to be the same. How then can you justify a comparison of your own results with those of others, unless they have first been subjected to vigorous statistical scrutiny. To base extensive arguments on such differences, without adequate statistical analysis of your data, is wasting a good deal of your own time and energy.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): In regard to statistics, I agree entirely with the criticism expressed. I dislike statistics because they can so readily be used to prove anything the speaker desires to prove.

Much stress has been laid upon the presence of a protective mechanism in regard to vitamins. Our observations in regard to vitamins are in agreement with these findings as noted in the body of the paper. As a matter of fact, the whole treatment for hemorrhage which I have outlined is based on the fact that nature has provided a protective mechanism which acts as soon as an ulcer begins to bleed and which must not be interfered with to get the best results. I have pointed out that the general weakness, the diminished blood volume and reduced blood pressure are important factors in permitting formation and organization of a thrombus in the bleeding vessel and that it is unphysiological suddenly to increase blood volume and pressure by means of transfusion or other intravenous injections. Iron medication has been found usually unnecessary because blood regeneration takes place naturally and rapidly without it. Even late transfusions, formerly recommended, have been found rarely necessary or of value.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): This symposium has been an instructive one. Discussion relative to treatment can readily terminate in a "free for all" because there is such a difference of opinion as to what constitutes the most effective procedure. Doctor Andresen's method, like anything he advocates, has its excellent points. The majority of the reports bearing on the results of the Meulengracht regimen or its modifications, are highly favorable to it, yet some discriminating clinicians are not ready to accept it and in fact feel that it is contraindicated under certain circumstances.

Knowing Doctor Hollander as I do, I feel sure that he did not mean to give the impression that statistics are useless and misleading. When scientifically compiled they are essential to medical progress. We have ourselves appreciated the importance of a full time statistician. The necessity for scientific statistical surveys is seen with reference to the subject under discussion. Data bearing on mortality from gastro-enteric hemorrhage are in a hopeless muddle, as you all know. This is largely due to the fact that calculations are based on all degrees and types of bleeding. A start in the right direction can be made by confining our observations to individuals who had

massive hemorrhage, the criteria for which have just been laid down by Doctor Blackford.

DR. JOHN M. BLACKFORD (Seattle—Closing): The discussion of the value of vital statistics has interested me much, because I am fully aware of the difficulties one may get into in the interpretation of statistics.

In replying to Dr. Eusterman's remarks, I would state that I agree with him fully in principle. Nevertheless, I must state again that the clinical records of these 55 deaths taken from the Bureau of Vital Statistics were reviewed by us almost as carefully as we might have reviewed the records of Dr. Eusterman himself. If I had gone back to Dr. Eusterman's records of such cases as I did in the instances taken from Vital Statistics, I would feel that I had approximately accurate and final information. It would make little difference where the cases came from if the records were fairly complete; for hospital records, whether from Seattle or from Rochester, must be more or less accurate:—50 of our 55 patients recorded in Vital Statistics died in hospitals.

We happen to have in Seattle three excellent pathologists who did postmortem examinations on 43 per cent of the Vital Statistics cases. I think this audience knows fully about the limits of clinical error in the diagnosis of the source of gastric hemorrhage; you know that with a clinical diagnosis of ulcer various authors estimate the error between 10 and 20 per cent. Certainly the maximum error in our cases should not be over 10 per cent, if 20 per cent is the maximum error, for the autopsy findings must be accepted in the 23 cases in which autopsy was done.

In 51 patients included in our series taken from Vital Statistics, chronic peptic ulcer was the only lesion; 49 of the 51 died above the age of 45 years. That ratio, whether

taken from vital statistics or from the Mayo Clinic or from Seattle, should be the same. We have shown by tabulation of all cases that the distribution by age is as stated.

Dr. Miller remarked on the larger mortality he has found in younger patients studied from Philadelphia records. I would strongly suspect that he has included surgical with his medical mortality, and that somewhere in Philadelphia we may have some surgical enthusiasts operating upon younger patients for massive hemorrhage.

Dr. Kantor has asked for the reason for operation. I apologetically stated that we had operated on some younger patients; and then remarked that we had lost two older patients following operation. The patients operated upon in our vital statistics series were all in the older group, and all were operated upon after waiting from one to three weeks. Such delay, in our experience (based on vital statistics experience and our own hospital experience) has been almost always fatal.

I feel most emphatically that the evidence shows that massive gastric hemorrhage from peptic ulcer occurring between the ages of 50 and 70 carries a mortality rate of approximately 30 per cent; or if the mortality percentage is based on all active gross hemorrhage from peptic ulcer in this older group, then the figure is approximately 15 per cent. Many of these fatalities should be spared by proper surgery. It seems to me that the tragedy of a massive hemorrhage from peptic ulcer in a person between 50 and 70 years of age must be compared with that of the hemorrhage from a ruptured liver or spleen. Serious hemorrhage from any of these sources seems to me an indication for exploratory operation. Certainly delay for many days after great loss of blood and then operation has resulted in terrific mortality. If operation is to be considered it should be done promptly after transfusion.

Some Unusual Gastro-Enterological Surgical Problems*

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ANY discussion of the diseases of the gastro-intestinal tract obviously centers about methods of treatment for the condition whether for functional or organic disease. Any method of management may be directed toward correction of altered physiologic or actual pathologic changes. The treatment of such recognized alterations from the normal, whether medical or surgical in their application, has been with few exceptions, accurately established and practiced by gastro-enterologists and surgeons. However, some pathologic processes have proved to be peculiarly unsuited to any form of direct attack such as surgery, principally because of poor results and because of the high mortality attendant upon any attempt at surgical management. Within the past few years the surgical treatment of such lesions of the gastro-intestinal tract heretofore considered inoperable has been made possible by virtue of improvements in surgical technique and of improvements in anesthesia. Certain highly technical operations designed for such problems have become justifiable because of an increasingly high

percentage of successful results and because of the lowered operative risk. Such surgical procedures to be justifiable, then, must be so planned and executed that one may offer the patient a better than reasonable chance of relief of distress, a distinct possibility of cure or at least a prospect of prolongation of life without disturbing gastro-enterologic symptoms and, above all, without prohibitive operative risk.

We will discuss in this paper some of the advances made in the surgical management of certain lesions of the gastro-intestinal tract. We wish to include in this group a plan for the management of large gastro-jejuno-colic fistulas, the problem of total gastrectomy for malignancy of the stomach, a method of resection for carcinoma of the lower end of the esophagus, together with some unusual surgical problems of the duodenum and jejunum.

It is unnecessary to point out that such highly technical surgical procedures require not only considerable experience and technical ability on the part of the surgeon but also the collaboration of a skilled internist in the selection of cases. Boldness and skill must be tempered by sound judgment on the part of

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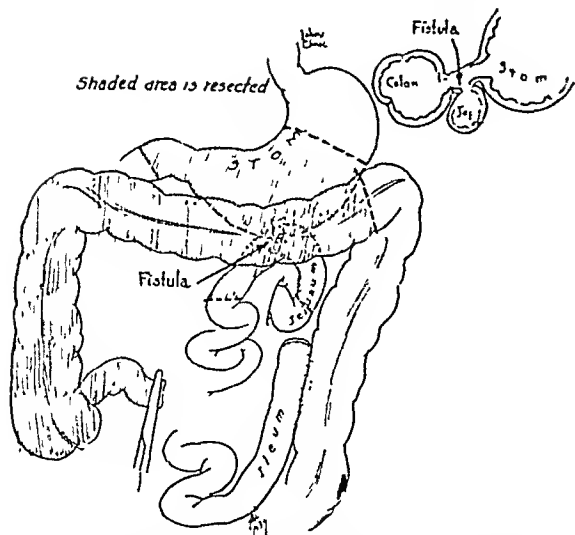


Fig. 1. Gastrojejunocolic fistula. Method of surgical management, first stage of operation. Terminal ileum is divided and ends of bowel closed by inverting sutures. A lateral anastomosis is made between proximal loop of divided ileum and a portion of the colon distal to fistulous communication. The shaded area of stomach and intestine illustrates portion to be resected at second stage. Insert shows relationship of fistula to stomach, jejunum and colon.

both internist and surgeon and results must certainly justify the selection of cases. Rash surgery can hope only to discredit both and cannot be too vigorously condemned.

One of the most serious complications of gastrojejunostomy has been the occurrence of gastrojejunocolic fistula. This lesion commonly follows the development of a jejunal ulcer at the site of the gastro-enterostomy stoma. The ulcer erodes and finally perforates into the adjacent transverse colon, producing a fistula leading from the colon into the jejunum and stomach. Many technical procedures have been proposed and performed to deal with such a fistula but all have been accompanied by an unduly high mortality because of the considerable risk of peritonitis from opening into a transverse colon filled with highly infective liquid contents. One of the most frequently employed methods of surgical management has been lysis of the fistulous tract, that is, to remove the tract and to restore normal gastro-intestinal continuity. This procedure not only carries with it the grave possibility of peritonitis but also, with restoration of normal gastro-duodenal continuity, reactivation of an old duodenal ulcer frequently occurs, the control of which still presents a serious problem.

The ideal surgical procedure, then, should include removal of the fistula as well as high resection of the stomach for control of the primary lesion, that is, the peptic ulcer which marked the beginning of the patient's difficulty. With this idea in mind, we have recently successfully employed a method embodying the safe removal of the fistulous tract together with high resection of the stomach. The operation has been performed in stages, with an interval of two weeks between stages. The first procedure consisted of division of the terminal ileum 6 inches from the cecum with closure by inversion of the ends of the proximal

and distal loops of ileum. An ileocolostomy, employing a lateral anastomosis is then made between the proximal end of the divided ileum and the transverse colon distal to the fistulous opening (Fig. 1). The purpose of this procedure is to permit emptying of the contents of the small bowel into the colon beyond the fistulous opening, reducing thus the colonic contents regurgitating into the stomach and at the same time establishing the fecal stream so that the colon with its contained fistula, jejunum and stomach may be resected in one block, thus avoiding peritoneal contamination.

Two weeks later a resection of the cecum with the small part of attached ileum, the ascending and transverse colon to a point beyond the fistulous communication, is carried out. Combined with this, high resection of the stomach is done and at the same time the affected jejunal loop is resected and an end-to-end anastomosis is made to reestablish jejunal continuity. These involved viscera are removed in one block without separating them. After resection of the stomach, the jejunal loop distal to this anastomosis is employed to form the gastrojejunal anastomosis (Fig. 2). The postoperative course has proved to be extremely uneventful; the patient improves rapidly and without the grave risk of a fatal peritonitis. We believe two factors influence the safety of such a method of surgical management; first, the change in the contents of

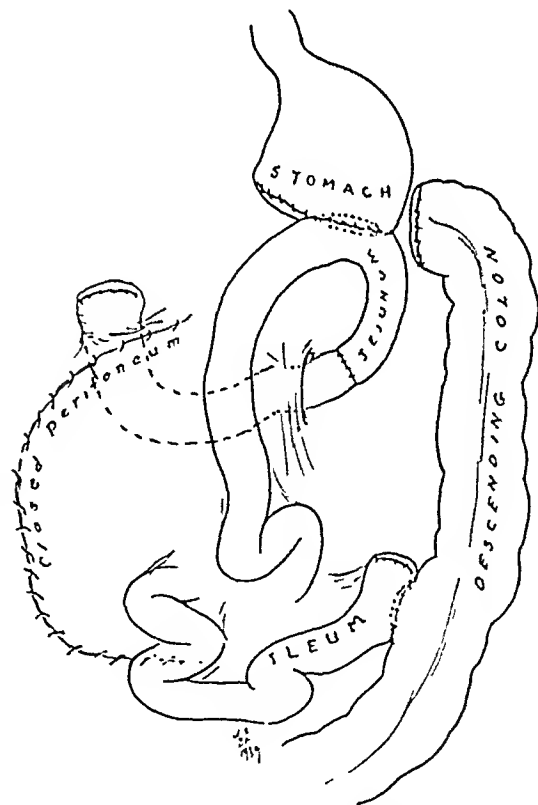


Fig. 2. Gastrojejunocolic fistula; second stage of operation; operation completed. Right colon and transverse colon to a point beyond fistulous tract are resected. Involved jejunum is excised and end-to-end anastomosis of jejunum is done. A high resection of stomach of the Hofmeister type completes the operation. The involved viscera are removed in one block.

the transverse colon, resulting from sidetracking of the fecal current, thereby reducing the opportunity for peritonitis, and second, the production in the peritoneal cavity of a certain degree of immunity to colon organisms by the first operation. The second stage which may be an extensive procedure is not an insurmountable operation and can be performed without gross contamination of the peritoneal cavity, which is certain to occur if a functioning large bowel is opened as it must be in separating the jejunum or stomach from the colon by any plan which attempts to close the fistula into the colon by direct approach to it.

to the splenic flexure and then rapidly filled the stomach.

Operation was advised and carried out in two stages. The first stage of the procedure was performed through a right rectus incision at which time the terminal ileum was divided 6 inches from the cecum. The ends of the ileum were closed by inversion and a lateral anastomosis was made between the proximal end of the divided ileum and the descending colon. Convalescence from the first operation was uninterrupted. Two weeks later, through a high left rectus incision, the right part of the colon and transverse colon to a point well past the fistula were resected. The loop of involved jejunum was then resected and an end-to-end anastomosis of jejunum was done. The

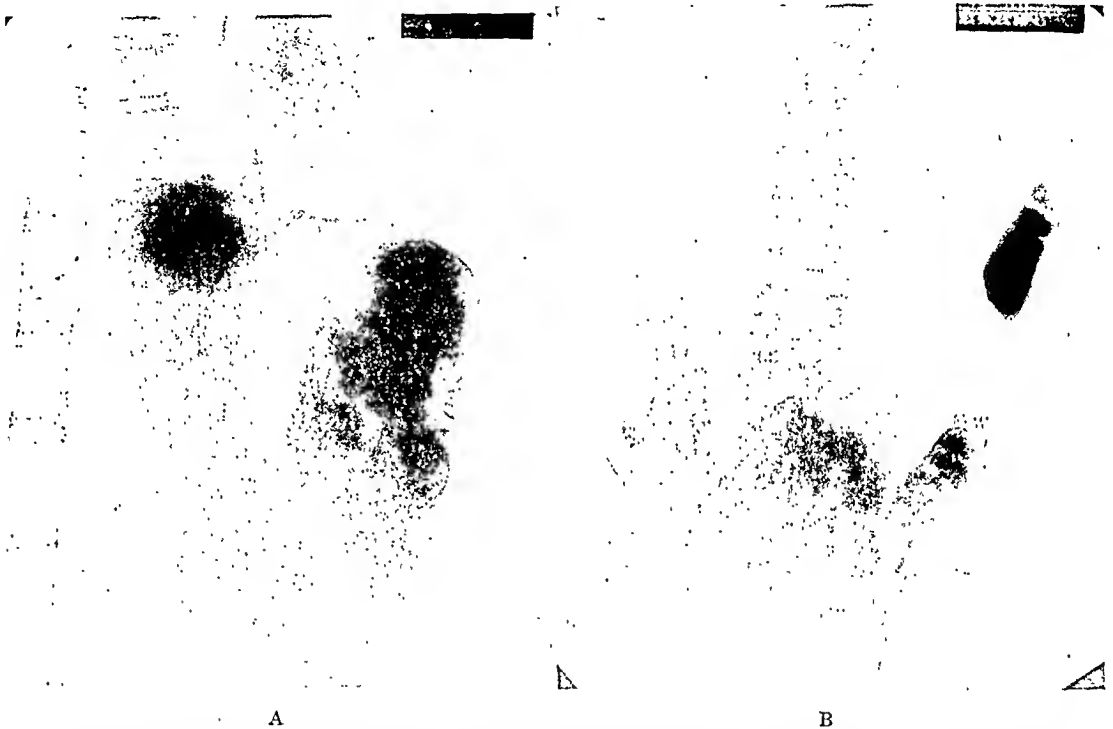


Fig. 3. Gastrojejunocolic fistula. Roentgen examination one year following operation. *a*, Roentgenogram of stomach following barium meal shows a gastric stump, one-fifth the size of the normal stomach. There is a good functioning stoma and little dilatation of the jejunum. *b*, Roentgenogram following barium enema. Barium is seen in the loops of ileum and the level of the ileocolic anastomosis is shown. Note that no barium goes beyond the splenic flexure of the colon.

The following case report is an example of the surgical management of gastrojejunocolic fistula.

CASE REPORT

A man, aged forty-three years, was first admitted to the clinic March 28, 1938, complaining of diarrhea and abdominal pain. He gave a history of acute perforation of a duodenal ulcer in 1918; gastro-enterostomy had been done elsewhere in 1929 for the relief of ulcer distress. Three years before admission to the clinic diarrhea was noted with seven to eight liquid stools daily. In the last year with continuation of diarrhea, undigested food was noted in the stools. Diarrhea occurred soon after meals. He also had some pain in the upper left part of the abdomen.

Physical examination revealed an essentially normal individual with the exception of rather marked undernourishment. A gastrojejunocolic fistula was readily demonstrated by fluoroscopic and roentgenologic examination; barium passed readily to a point 4 inches proximal

operation was completed with removal of four-fifths of the stomach and the formation of an anastomosis between the jejunum and the resected stomach.

Convalescence following this extensive procedure was entirely uneventful and the abdominal incision healed cleanly. The patient was discharged eighteen days after the second operation in excellent condition, with no dietary difficulties on a liberal regime. He was again examined one year after operation; he had gained 18 pounds, had no abdominal distress and had had no diarrhea (Fig. 3).

The problem of management of malignant lesions of the stomach by surgical measures is admittedly a perplexing one, yet the difficulty arises not so much from a technical viewpoint but more frequently as the result of delay in submitting patients with gastric lesions to operation. Naturally, this is a problem of early diagnosis which may depend upon a number of factors not directly under the control of the physician. Without



Fig. 4. Linitis plastica. Annular filling defect occupies the middle two-thirds of the stomach. Peristaltic waves are absent and defect is constant. Operation, total gastrectomy.

question, in recent years the field of gastric surgery as pertains to both ulcer and cancer has been greatly widened through improvement in technic. Problems of greater magnitude are successfully managed and a more aggressive attitude toward these lesions is justifiable upon the basis of results obtained. One need not necessarily speak in terms of cure of widespread malignant disease of the stomach but rather in terms of the alleviation of distress and prolongation of life which can be confidently predicted by surgeons experienced in gastric surgery. Total gastrectomy has been performed many times successfully and with satisfying results. Life has been prolonged, abdominal distress alleviated, with an ever decreasing operative risk, as well as in the vast majority of cases, an astonishingly low postoperative morbidity and freedom from postoperative distress.

One must admit that the number of patients upon whom a total gastrectomy is justifiable is limited; also, one cannot confidently determine from the clinical data and from roentgenologic evidence the patients upon whom total gastrectomy is possible. One can frequently suspect from data obtained by examination that if resection is possible the entire stomach must be removed. The gastric lesion which requires total gastrectomy involves most of the stomach and most frequently is the type described as a diffuse fibrocarcinoma of the stomach or linitis plastica. This tumor extends by infiltrating the walls of the stomach, producing a rigid diffusely thickened gastric organ, and can frequently be suspected from fluoroscopic examination of the stomach. This type of malignant disease is well recognized and the indications for complete removal quite well established.

The following case report is an excellent example of a diffuse malignant process involving the whole stomach, for which total gastrectomy was done.

CASE REPORT

A man, aged forty-six years, was admitted to The Lahey Clinic, March 6, 1939, complaining of epigastric distress of one year's duration. This distress was frequently associated with nausea and vomiting and during the year he had lost 10 pounds. Anorexia and a tendency to fatigue were noteworthy symptoms. He had had roentgenologic examination of his stomach twice before admission to the clinic, without a definite diagnosis being made.

Examination revealed an undernourished individual with scaphoid abdomen. A tumor mass was readily palpated in the epigastric region. Analysis of gastric contents revealed absence of free hydrochloric acid and the presence of erythrocytes. Roentgenologic examination of the stomach demonstrated a large filling defect involving the media of the stomach (Fig. 4). Barium passed rather quickly through the constricted region and the stomach was completely emptied in three hours. No evidence of metastasis could be found upon careful physical examination, and exploratory operation with resection of carcinoma of the stomach was advised.

Operation was performed March 23, 1939, at which time a stomach rigid from malignant infiltration of the walls was found, a typical linitis plastica. The entire stomach was involved and except for several small glands noted along the greater curvature, no evidence of metastatic spread of the tumor could be found. The stomach was completely removed and a loop of jejunum was brought anterior to the colon and anastomosed to the end of the esophagus (Fig. 5).



Fig. 5. Roentgenogram following total gastrectomy. The barium outlines the esophagus and passes readily into the jejunum. The esophagojejunal anastomosis is shown at the level of the diaphragm.



Fig. 6. Carcinoma of cardia of stomach. Roentgenogram shows a bulky adenocarcinoma involving the cardia of the stomach and extending into the lumen of the esophagus. Operation, total gastrectomy.

Convalescence was uninterrupted and the patient was discharged eighteen days later, at which time he was able to take a satisfactory diet.

Total gastrectomy may also be employed with quite satisfactory results in other types of gastric malignant disease. One of us (1) has described complete removal of the stomach for leiomyosarcoma in a woman, twenty-seven years of age, who is alive and quite well one and a half years after operation. This tumor was of relatively low malignancy and had not spread beyond the walls of the stomach. We have (2) recently had another type of malignant tumor, a malignant lymphoma, which diffusely infiltrated the mucosa and the submucosa of the entire stomach, which did not penetrate the muscular layers and which stopped sharply at the duodenal and esophageal borders. This tumor occurred in a woman of thirty-two years. The stomach was thickened and rigid and in this case total gastrectomy was also successfully performed. The patient made a most uneventful recovery and was discharged from the hospital seventeen days after operation, upon a fairly liberal diet.

Another form of malignant involvement of the stomach which frequently lends itself quite satisfactorily to total resection is carcinoma of the cardia of the stomach. We have recently had two patients with large tumors of the cardia which had grown locally and which had not yet involved the diaphragm, liver, and other organs. These tumors were successfully removed by total resection, anastomosing the jejunum to the esophagus after the technic which we

have described (3). An illustrative case report of successful total resection of the stomach for a large carcinoma of the cardia is given below.

CASE REPORT

A man, aged fifty years, was admitted to the clinic November 25, 1938, complaining of difficulty in swallowing of thirteen months' duration. Swallowing was accompanied by soreness and pain in the epigastrium. The symptoms had increased in severity the last few months. He had lost 10 pounds. Roentgenologic examination done a month before admission showed delay in the passage of barium, which was interpreted as cardiospasm.

Physical examination at the clinic revealed an irregular mass involving the medial portion of the cardia of the stomach and extending into the distal portion of the esophagus (Fig 6). The remaining portion of the stomach and duodenal bulb were normal. Erythrocytes numbered 4,510,000 and the hemoglobin was 71 per cent.

At operation, November 29, 1938, a tumor mass was found which was as large as one's fist (approximately 8 cm. in diameter), and occupied the cardia of the stomach. No obvious gland involvement or distant metastasis could be demonstrated. Total resection of the stomach was carried out without difficulty and the esophageal stump was anastomosed into the lateral border of a loop of jejunum. The pathologist's report was adenocarcinoma of the cardia of the stomach with metastasis to two of fifteen lymph nodes.

The patient's postoperative reaction was extremely mild and he was discharged twenty days after operation upon a liberal diet and with no difficulty in swallowing.

One is not justified in refusing operation to patients with malignant disease arising in the cardia, and certainly with failure to demonstrate extension or metastasis, exploratory operation should be carried out in all cases with the hope of possible successful removal by complete gastrectomy. Whatever the findings, in the presence of obstruction to the lower end of the esophagus, some type of gastrostomy can be performed. Furthermore, as is discussed later, removal of the tumor even in the face of esophageal involvement is possible by means of a transpleural approach. It must be emphasized that the gastric malignant lesion inexorably progresses to a fatal outcome without surgical interference and any procedure which widens the scope of attacking the disease is a worthy one. In The Lahey Clinic, we have performed total gastrectomy in nineteen cases, with an operative mortality in five cases; two fatalities have occurred in the last ten total resections of the stomach done in the clinic.

It is of value at this point also to comment upon the importance of preoperative preparation in relation to morbidity and mortality which may follow such extensive technical procedures upon the stomach. For a period of more than two years all patients with gastric carcinoma have been prepared for operation by thoroughly washing the stomach with dilute hydrochloric acid the night before and in the morning immediately before operation. The bacterial counts as plated upon Petrie dishes have been reduced many times and in many cases, a sterile content of the stomach has been demonstrated.

The surgical removal of carcinoma of the lower end of the esophagus presents a somewhat more difficult problem than that associated with gastric malignant lesions. The question of successful removal is influenced by the inaccessibility of the lesion and by extension of the tumor to surrounding structures due to

delay in diagnosis and in advising treatment. Unfortunately, most of these patients are not referred to the surgeon until marked malnutrition has occurred as a result of obstruction of the esophagus. Ewing has drawn attention to the fact that carcinoma of the esophagus has a tendency to metastasize early because of the abundant blood and lymphatic supply and because of vigorous esophageal movements resulting from swallowing.

Very few cases of successful resection of this region, in which normal esophageal gastric continuity

cision, mobilizing the lower part of the esophagus in the thoracic cavity and exposing the stomach through a radial incision through the diaphragm (Fig. 7). After the cardia of the stomach is mobilized, the tumor is resected, together with a generous border of normal tissue on either side of the tumor. This necessitates removal of a portion of the cardia of the stomach as well as a portion of the esophagus. The stomach is then brought partly into the thoracic cavity to bridge the gap caused by removal of a segment of esophagus, and the divided end of the esophagus is

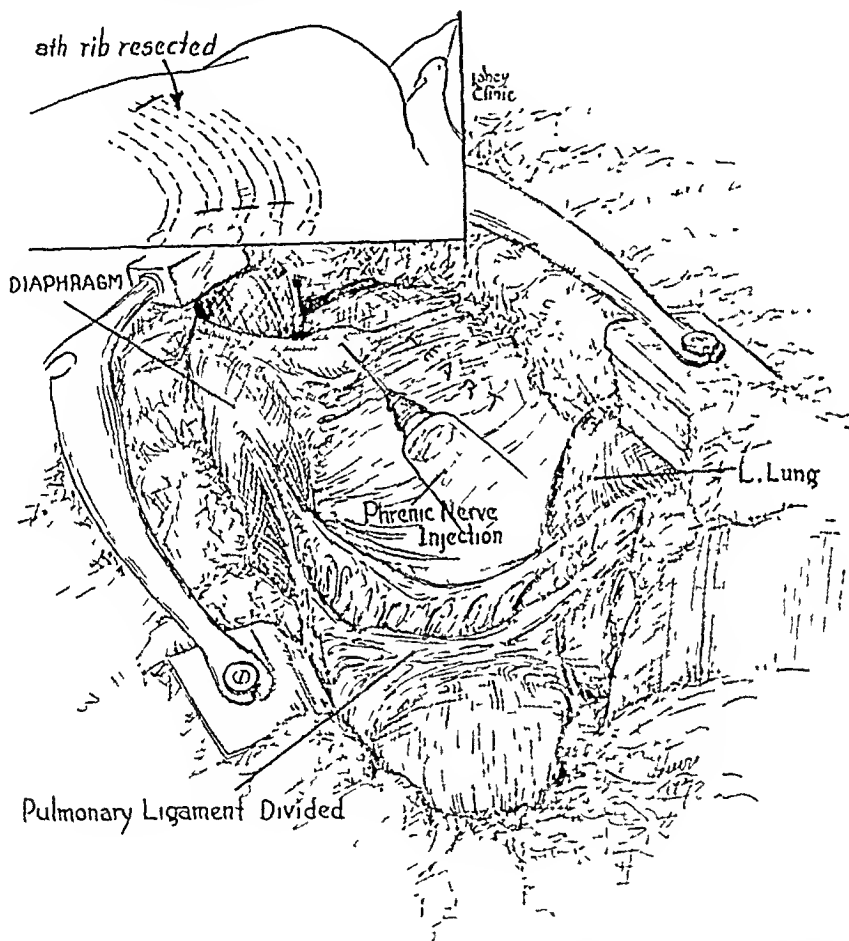


Fig. 7. Carcinoma of esophagus, lower third. Operation, transthoracic resection. Left thoracic cavity is opened through an infrascapular incision. *Insert*, eighth rib is resected and the seventh and ninth ribs are divided posteriorly. The inferior pulmonary ligament is divided and the left lung retracted, exposing diaphragm and mediastinum. The left phrenic nerve is infiltrated with novocain solution, 2 per cent.

has been established, have been reported in the literature. We have recently reported an example of successful resection with reestablishment of normal swallowing (3). Since this report, we have performed an exploratory operation in two other cases but were unable to resect the malignant tumor because of metastasis to the pleura in one case and in another because of extension to retroperitoneal glands. Resection has been carried out in three other patients, with one death after operation. The operation is performed through a left, infrascapular transpleural in-

implanted into the anterior wall of the stomach (Figs. 8 and 9). The rent in the diaphragm is then closed snugly about the stomach to prevent any herniation of abdominal viscera, thus making the stomach partly intrathoracic. The surgical management of these cases involves a considerable technical procedure but can be performed with a reasonable expectancy of success.

CASE REPORT

A man, aged forty-six years, came to the clinic July 29, 1937, because of pain in the epigastrium noted when swallowing food. The symptoms were of nine months'

duration and he had gradually limited his food to liquids and soft foods.

Other than evidence of loss of weight, the patient's general condition was good. Roentgenologic examination had revealed an obstruction at the lower end of the esophagus and microscopic examination of a specimen obtained from the tumor through an esophagoscope showed it to be an adenocarcinoma.

Operation was performed July 31, 1937, at which time, with the patient in the left lateral position, a long infrascapular incision was made on the left side parallel to the ninth rib, the trapezius was divided, the scapula elevated and the ribs exposed. The entire length of the ninth rib was removed, the eighth and tenth ribs were divided near the proximal ends and the pleura opened. The in-

Following operation convalescence was stormy but the patient finally recovered and was discharged to his home, able to swallow quite normally. Fifteen months later after a fairly comfortable existence he died following recurrence of the tumor.

It is apparent that the patients to be submitted to such an extensive operation should be selected with great care. The collaboration of the internist, roentgenologist and surgeon is absolutely necessary. Obviously, any evidence of metastasis contraindicates surgical interference designed to remove the tumor. Evidence of a high degree of obstruction will in most cases indicate wide extension of the tumor and will

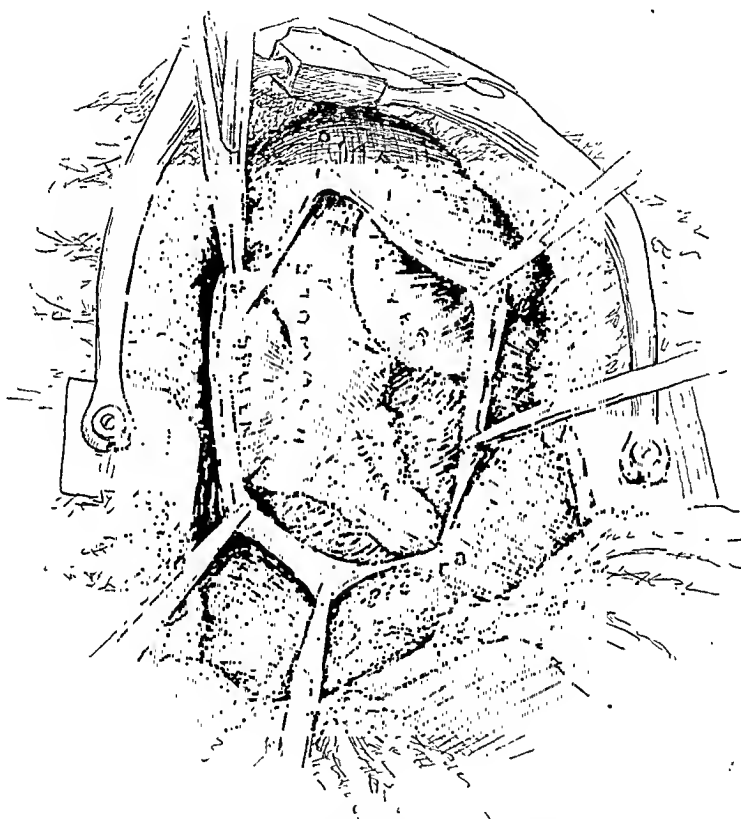


Fig. 8. Carcinoma of esophagus, lower third. The parietal pleura is incised exposing the esophagus and tumor. Diaphragm is opened radially in line of its muscle fibers showing the relationship of esophageal tumor to stomach and to liver and spleen.

ferior pulmonary ligament was divided and the lung retracted. The left phrenic nerve was injected with novocain and the esophagus exposed by incising the pleura over it. The diaphragm was then opened. The stomach was mobilized along its borders by dividing its attachments. The segment of esophagus containing the tumor was removed with the upper portion of the stomach, allowing a wide margin on either side of the tumor. The open end of the stomach was then closed by over and over catgut stitches and inversion completed with interrupted black silk stitches. The stump of the esophagus was then transplanted into the anterior wall of the stomach. The rent in the diaphragm was closed about the stump, thus making the stomach partly intrathoracic to bridge the gap caused by removal of the esophagus and part of the stomach, thus restoring gastro-esophageal continuity.

usually indicate an irremovable malignant tumor. Metastatic extension will involve not only local glands but very early will extend to glands along the lesser curvature of the stomach and to the retroperitoneal glands posterior to the lesser omental cavity. All patients should be examined under the fluoroscope and esophagoscopy should be performed to obtain a section of the tumor for microscopic examination before operation is advised.

The number of patients who have carcinoma of the lower third of the esophagus and upon whom such a procedure can be carried out is naturally limited, yet this operation offers a method of handling such patients who otherwise would go on to early death

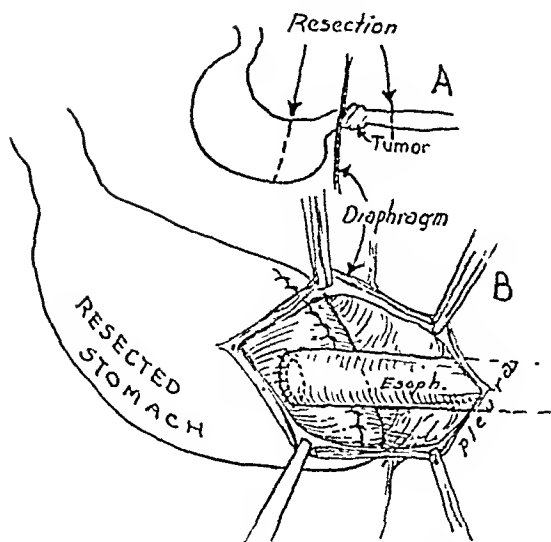


Fig. 9. Carcinoma of esophagus, lower third. *a*, Illustrating portion of stomach and esophagus containing tumor to be resected. The divided end of the stomach has been inverted. The esophageal stump has been transplanted into the anterior wall of the stomach, reestablishing continuity of esophagus with stomach. The stomach is brought partly into the thoracic cavity to bridge the gap caused by removal of a portion of the esophagus. The rent in the diaphragm is closed about the stomach.

unless an effort were made to remove the malignant tumor. One patient lived fifteen months, was able to swallow normally and was quite comfortable until the tumor recurred. In the other cases the operation was done too recently to be worth considering from the standpoint of prolongation of life or otherwise, yet in each case normal swallowing was possible.

This procedure can also be employed in patients in whom the malignant lesion arises in the cardia of the stomach and extends into the esophagus. One of our patients presented such a problem. The technical procedure is no more difficult because of this origin. This simply means that a somewhat greater segment of stomach must be taken. The stomach can be mobilized satisfactorily through the rent in the diaphragm and can be brought into the thoracic cavity to establish the esophageal gastric anastomosis.

Another problem of interest to the gastro-enterologist and somewhat less so to the surgeon is the matter of treatment of diverticula of the duodenum. Duodenal diverticula are not uncommonly demonstrated by roentgenologic examination of the duodenum, carried out in routine studies of the gastro-intestinal tract. They occur most frequently in the second part of the duodenum, near the ampulla of Vater or duct of Santorini, and commonly are noted upon the concave border of the duodenum. The next most frequent location is in the third part of the duodenum. They rarely are noted in the first part unless they appear as simple outpouchings of the duodenal wall, associated with duodenal ulcer.

Gastro-intestinal symptoms resulting from the presence of duodenal diverticula are not characteristic of the lesion and probably most diverticula do not give rise to symptoms. Gastro-intestinal distress arising in

the presence of a demonstrable duodenal diverticulum are those probably of an associated pathologic process resulting from disease of the gall bladder, ulcer or pancreatitis. Consequently, very few diverticula, duodenal in origin, will require operation to alleviate distress.

Inflammation arising in such diverticula, associated with delay in emptying the sac or due to irritation of contents of the sac or pressure of the filled sac upon the surrounding viscera, probably accounts for the symptoms noted. This distress commonly comes on a half hour or more after meals and may be confused with ulcer pain. The most common complaint is epigastric pain or heaviness, and nausea which may be associated with vomiting. Since the symptoms are not characteristic, the diagnosis must be made from roentgenologic findings. The treatment after ruling out all other causes for the abdominal discomfort, is medical, principally the employment of a nonirritating bland diet and various alkaline powders.

Very few patients with diverticula of the duodenum will need to be subjected to operation. Those on whom operation is carried out usually have large diverticula to which apparently the distress can be traced directly and which are thought to be chiefly responsible for the patient's symptoms.

Any operation upon a duodenal diverticulum may involve considerable risk because of the difficulty in exposing such a sac, which usually arises from the



Fig. 10. Diverticulum of duodenum. Roentgenogram shows duodenal cap well filled, smooth and symmetrical. The second part of the duodenum is narrowed, while posterior to and above the duodenum there is a large mass of barium which occupies a large diverticulum of the duodenum. The dotted line outlines the diverticulum.

second part of the duodenum and frequently is retroperitoneal in origin. One should, therefore, demonstrate in so far as possible that the symptoms arise from a diverticulum, that relief cannot be obtained from conservative medical measures, and before operation is advised one must be convinced from the location of the diverticulum that the lesion is in all probability safely removable. An illustration of such

a case in which operation was carried out is given below.

CASE REPORT

A woman, aged sixty-eight years, came to the clinic November 9, 1938. She had had epigastric distress of three weeks' duration. Pain was severe, occurred four hours after meals and was not relieved by soda or food. The pain was accompanied by slight flatulence but no nausea or vomiting. No weight loss was noted. Roentgenologic

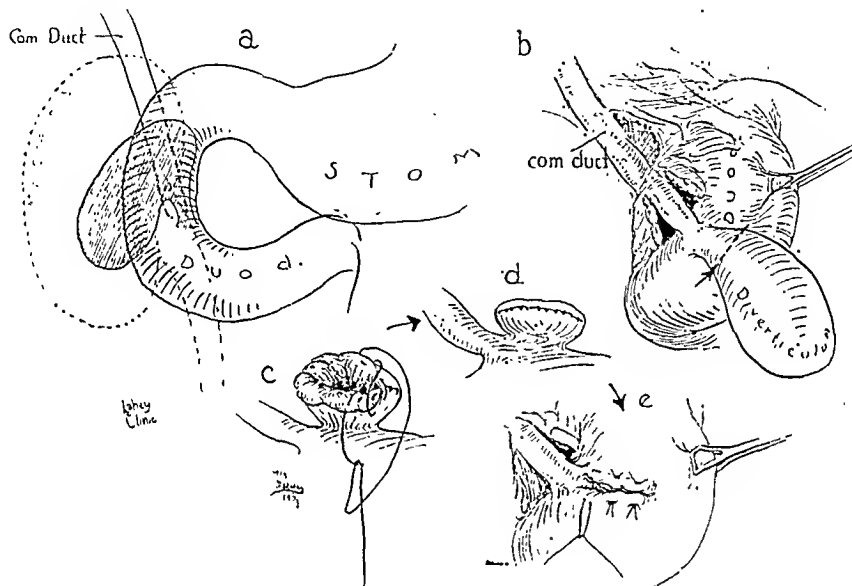


Fig. 11. Diverticulum of duodenum. Operation for removal. *a*, The relationship of diverticulum to duodenum, common bile duct and kidney is shown. *b*, The duodenum has been mobilized, the common bile duct and head of pancreas exposed. The diverticulum has been freed from surrounding structures. *c* and *d*, The diverticulum has been removed. The neck of the sac is closed by inverting sutures of catgut, reinforced with mattress sutures of silk.

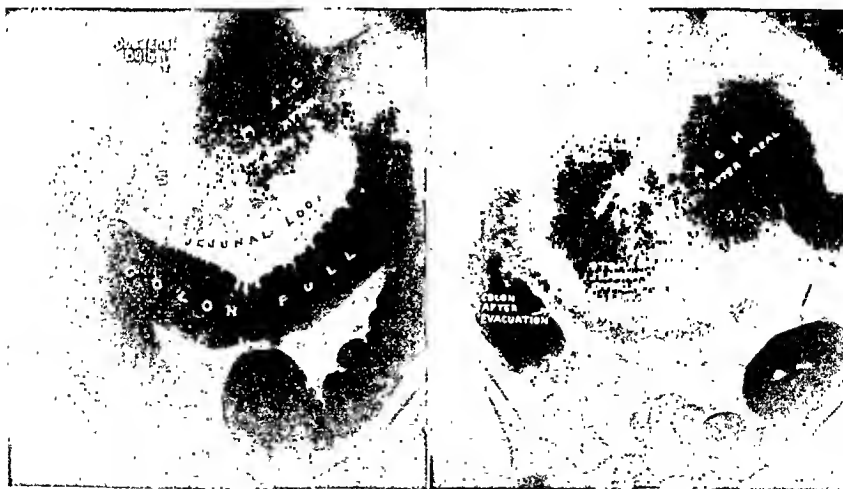


Fig. 12. Roentgenogram showing an obstructing lesion at the duodenojejunal junction as demonstrated by retained barium in a dilated stomach twenty-four hours following a barium meal. The duodenal cap, second and third portions of the duodenum are dilated three or four times their normal size. During the twenty-four hour period only a small amount of barium was seen to pass from the stomach into the dilated duodenum.

examination revealed that the duodenal cap filled well, was smooth and symmetrical. The second part of the duodenum was somewhat narrowed, while posterior to and above the duodenum there was a large mass of barium which had the appearance of a loop of intestine, but was located in the position of the gall bladder (Fig. 10). Cholecystograms were normal.

At operation, a very large diverticulum, 3 inches in diameter, was found arising from the posterior wall of the duodenum near the ampulla of Vater. The diverticulum lay posterior and lateral to the duodenum and was retroperitoneal. The sac was dissected free from the surrounding structures and was found attached to the posterior wall of the duodenum by a narrow neck. The diverticulum was removed, the neck of the sac ligated and inverted into the duodenal lumen, reinforcing the duodenal wall in this region with silk sutures (Fig. 11). Following operation the patient's course was afebrile, food

was taken without distress, and she was discharged from the hospital eighteen days after operation.

Tumors of the small bowel are of relatively infrequent occurrences and rarely present any great technical difficulty in their surgical removal, provided, of course, metastasis and extension permit resection. Kiefer (4) reported thirteen cases of tumor of the small bowel from The Lahey Clinic (1933) and in a later report Chamberlin (5) (1938) added nine cases. Of the total group of twenty-two cases, ten involved the jejunum. Malignant tumors of the jejunum may originate high in the jejunum or even at or just beyond the ligament of Treitz. Such a high origin of a malignant tumor in the jejunum may present a considerable problem in the surgical management because following resection of the segment containing the tumor, the remaining jejunal stump may be too short to make a satisfactory end-to-end anastomosis. When the tumor has been found to involve the jejunum at the ligament of Treitz the tendency has been to perform a transmesocolic anastomosis of the duodenum and jejunum and to make no attempt at removal of the malignant lesion. In spite of the level of origin of these tumors many prove resectable and the problem becomes a technical one, that of reestablishing a safe intestinal continuity. The case report given below illustrates a method devised and employed by one of us in handling successfully such a situation.

CASE REPORT

A woman, aged fifty-eight years, was seen in the clinic October 12, 1938, because of severe epigastric distress of six weeks' duration and vomiting for the last five days. Physical examination did not reveal tenderness, spasm or masses in the abdomen. Erythrocytes numbered 4,960,000 and leukocytes 5,000. On gastric analysis, the total acid was 20 and the free acid 7. Roentgenologic examination revealed an obstructing lesion at the junction of the duodenum and jejunum, without definite characteristics (Fig. 12). A diagnosis was made of jejunal obstruction probably due to carcinoma, and operation was advised.

October 17, a loop of jejunum 18 inches in length was resected and a side-to-side antecolic duodenojejunostomy was performed. The pathologist's report was adenocarcinoma; two lymph nodes which were removed with the specimen were reported to be normal. After removal of the segment of the jejunum containing the tumor (Fig. 13), the remaining intraperitoneal jejunal loop was too short to make a satisfactory and safe end-to-end anastomosis possible. The upper and lower ends of the remaining jejunum were closed by inversion with catgut, and reinforced with mattress sutures of black silk. The right hepatic flexure of the colon was then entirely mobilized and the transverse colon freed up to its middle portion (Fig. 14). The hepatic flexure was turned toward the midline and the retroperitoneal duodenum exposed and mobilized throughout its entire extent. An incision was then made in the ligament of Treitz, freeing the upper stump of jejunum which was reduced toward the right side beneath the root of the mesenteric vessel. The jejunal stump was thus entirely freed with its mesentery intact, brought over in front of the transverse colon and a lateral anastomosis readily made with the lower stump of the jejunum (Fig. 15). Following operation, recovery was uneventful, with no obstruction at any time and with complete and immediate establishment of the fecal stream.

SUMMARY

Some complicated gastro-enterologic problems with which we have had to deal are discussed and the plans which we have employed in their management are

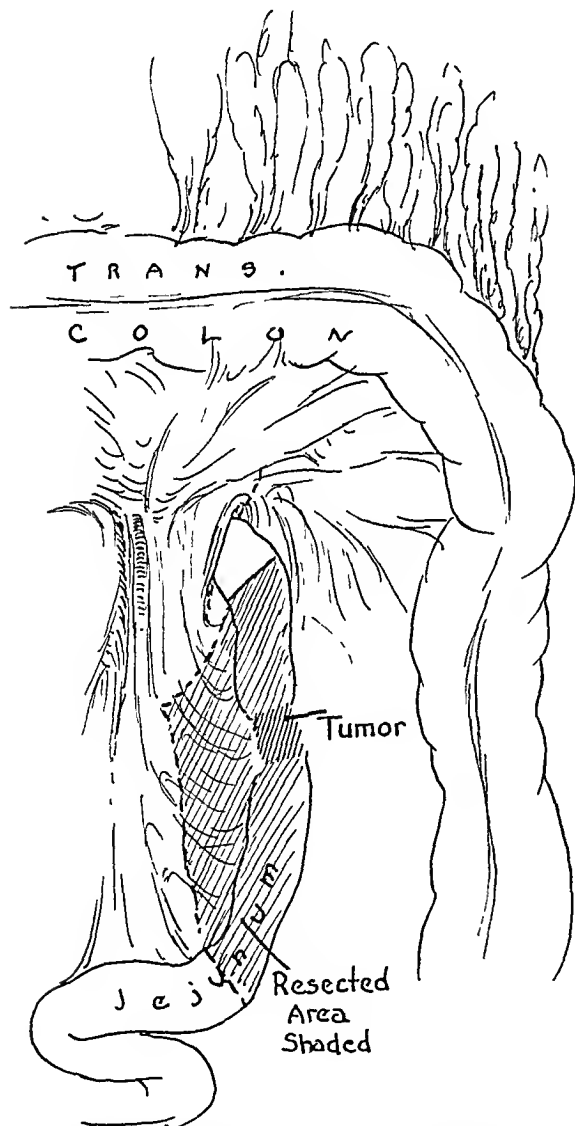


Fig. 13. Carcinoma of the jejunum. Drawing shows segment of jejunum with tumor. The relationship to the colon and Treitz ligament is illustrated.

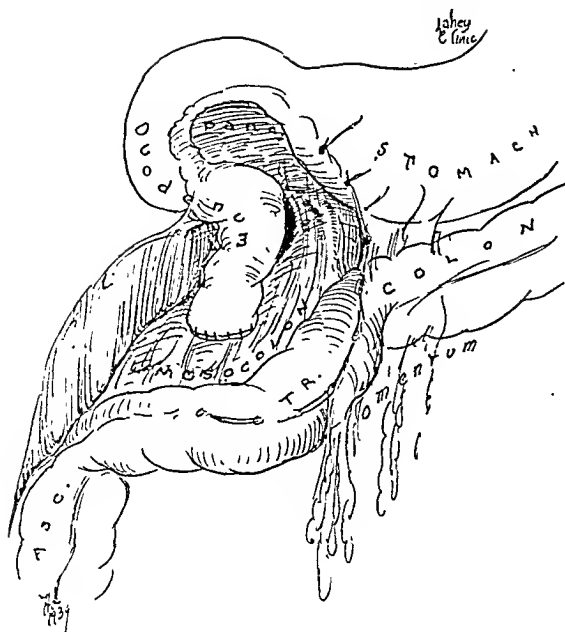


Fig. 14. Carcinoma of the jejunum. The hepatic flexure of the colon has been mobilized and the transverse colon also mobilized to its mid portion. The proximal end of the jejunum following resection of the tumor has been reduced beneath the root of the mesenteric vessel. The jejunal stump is thus freed with its mesentery intact and brought anterior to the transverse colon.

presented. These include a two stage plan which we have employed in the management of a large gastro-jejunal fistula; total gastrectomy for gastric carcinoma; experiences with transpleural resection of the lower end of the esophagus for malignancy with restoration of swallowing; the management of duodenal diverticula, and a plan for successfully restoring the fecal stream in high jejunal resection with a short jejunal stump.

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DISCUSSION

DR. SAMUEL F. MARSHALL (Boston): Mr. President and Members of the Association: Certainly an aggressive attitude in the surgical management of these cases is justifiable, but only if we can show a lowered morbidity and mortality. If an increased number of months or years of the patient's life can be obtained and relief of some of the disturbing symptoms results, certainly I think the surgical procedure is justifiable.

It has been proven quite conclusively that total gastrectomy can be done with a lowered mortality and with practically no morbidity following the operation. As Dr. Lahay has told you, we have done total gastrectomy in twenty cases with five deaths. In the last eleven cases two deaths occurred. One was in one of my cases in which I am sure that the operation was poorly chosen.

Several factors influence the lowered mortality and morbidity. Perhaps the outstanding and the most influential factor is the employment of nupercaine in spinal anesthesia. I am sure this has reduced the morbidity and lowered the mortality because this anesthesia produces better conditions for operation and pulmonary complications can be avoided.

An important factor which is always present and of which we are always aware is the experience of the surgeon.

Another factor I would emphasize is the employment of nonabsorbable sutures in carrying out extensive resections such as total gastrectomy.

Total gastrectomy can be done readily, particularly with the type of anesthesia we employ now. It is a painstaking procedure, but not a very difficult procedure. We do not think it necessary to divide the costal margin to get exposure.

The other problem that interests me, and which Dr. Lahay has presented to you, is resection of carcinoma of the lower third of the esophagus. As Dr. Lahay said, we are not prideful of the report of these cases, but we feel rather that they represent an advance. This procedure is not original but we hope at least to do something for these patients if we can get them early enough. They should be referred early enough to permit such a radical procedure to be carried out and the problem of early recognition belongs to the general practitioner.

I know that you are aware that carcinoma of the lower third of the esophagus metastasizes early and may involve the glands along the lesser curvature of the stomach. There is no possible way of telling the extent of metastasis until operation is performed.

Exploratory operation should be carried out trans-thoracically. It is a simple procedure. One rib can be removed, the lung retracted and the surgeon can determine if the case is operable.

We have had four cases in which carcinoma of the esophagus was removed. One death occurred which probably was due to the fact that the phrenic nerve was not permanently disabled.

This operation makes it possible to remove lesions of the esophagus if they are recognized early.

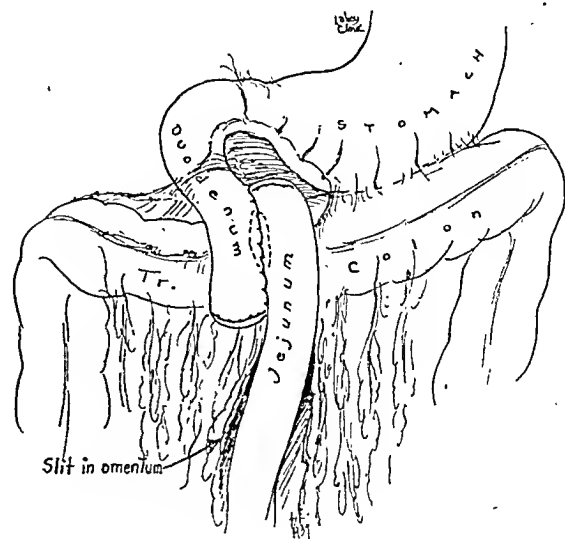


Fig. 15. Carcinoma of the jejunum. The omentum is divided vertical to its attachment to the transverse colon. The mobilized proximal jejunal stump is brought in front of the transverse colon and a lateral anastomosis is made with the lower stump of jejunum, thus restoring intestinal continuity.

Abstracts

BIBLIOGRAPHY ON NORMAL NUTRITION

Arranged by The American Dietetic Association, Community Education Section, 1938-39.

The purpose of this compilation is to meet the needs of members of the medical and dental professions, students and internes, who wish to know of books on nutrition so that they may keep abreast in this rapidly developing field. Some books have been included, of a more "readable" type, which may be recommended to the intelligent layman.

REFERENCE AND TEXT BOOKS ON NUTRITION

1. A Series of Articles on the Present Status of Our Knowledge of the Vitamins. Price \$2.50, pp. 580. Chicago: American Medical Association, 535 N. Dearborn St., 1939.

The articles in this series were prepared under the auspices of the Council on Pharmacy and Chemistry and the Council on Foods.

2. Nutrition and Public Health by Et. Burnet and W. R. Aykroyd (reprint No. 2 from Quarterly Bulletin of the Health Organization, League of Nations) June, 1935. Price \$0.50, pp. 152. New York: Columbia Univ. Press.

This report is addressed primarily to public health authorities. The data selected show the remarkable worldwide advances of the science of nutrition and its present problems. After introductory chapters on the problems which confront dietitians today and the fixing of dietary standards, the editors consider the world's food supply, its production, distribution and preservation, the influence of poverty and unemployment on diet, infant and child nutrition, the food deficiency diseases and have added an interesting study on collective feeding.

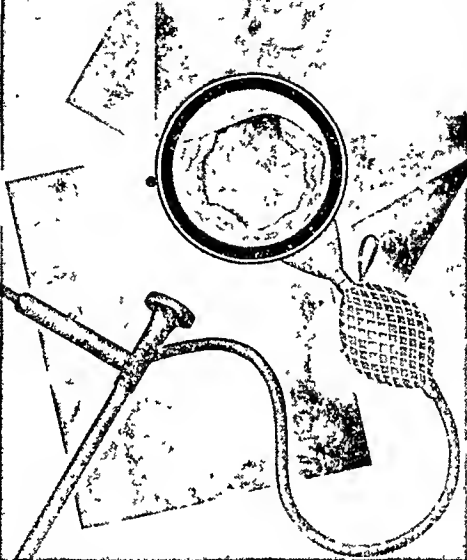
3. Nutrition of the Infant and Child. By Julian D. Boyd, B.S., M.S., M.D., Asso. Prof. of Pediatrics, State University of Iowa. Edited by Morris Fishbein, M.D. Price \$3.00, pp. 198, with 40 illustrations. New York: National Medical Book Co., Inc., 1937.

This monograph is a summary of nutrition in pediatrics. It is written from a critical viewpoint. The contents are divided into sections on the principles of nutrition, foods for the normal infant and child, and nutrition during illness. In a few pages at the end, practical diet lists and schedules are provided for normal infant feeding and for therapeutic dietetics.


4. Nutrition. By Margaret S. Chaney, Ph.D. Prof. of Home Economics, Connec. College, and Margaret Ahlborn, M.S., Prof. of Nutrition, Kansas State College. Price

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\$3.00, pp. 436. Boston: Houghton Mifflin Co., 1939.

A text book for college students in nutrition.

5. Nutrition in Health and Disease. By Lenna F. Cooper, Edith M. Barber and Helen S. Mitchell, Ph.D. Price \$3.00, pp. 708. Philadelphia: J. B. Lippincott Co., 1938.

A text and reference for physicians, students of nutrition and dietitians who teach nurses. The book is in seven parts, (1) normal nutrition, (2) diet in disease, (3) feeding of mother and child, (4) nutrition and the public health program, (5 and 6) food selection and cookery for normal

and for sick and convalescent and (7) an appendix.

6. The Avitaminoses. By Walter H. Eddy, Ph.D. and Gilbert Dalldorf, M.D. Price \$4.50, pp. 338. Baltimore: The Williams and Wilkins Company, 1937.

This book is the result of eight years of collaboration between Professor Eddy, a biochemist engaged in nutrition research and Dr. Dalldorf, a physician and pathologist. The purpose of the book is to call attention to pathological responses—sub-clinical and acute—to vitamin deficiencies in the diets of human beings as well as of experimental animals.

7. Vitamins in Theory and Prac-

tice. By Leslie J. Harris, Sc.D., D.Sc., Nutrition laboratory, Univ. of Cambridge and Medical Research Council. Price \$4.00, pp. 240. New York: The Macmillan Co., 1937.

Dr. Harris explains in entertaining and simple fashion how the various vitamins were discovered, and how they work in the human system.

8. Vitamins and Vitamin Deficiencies. I. Introduction and Historical, Vitamin B, and Beri-beri. By Leslie J. Harris. Vol. 1, pp. 218. London: J. and A. Churchill, 1938.

This volume, which has a foreword by F. G. Hopkins, is the first of a series planned to provide a comprehensive synopsis of the results of modern research on each of the known vitamins.

9. Biochemistry for Medical, Dental and College Students. By Benjamin Harrow, College of City of New York. Price \$3.75, pp. 385. Philadelphia: W. B. Saunders Co., 1938.

The latest developments in the field of animal biochemistry are contained in this text book. One of the 24 chapters is devoted to a discussion of the biochemical aspects of the nervous system and another to the hormones in connection with the glands which manufacture them. The appendix contains tabular data on the nutritive value of foods.

10. The Newer Knowledge of Nutrition. By E. V. McCollum, Ph.D., Sc.D., Prof. of Biochemistry: Elsa Orent-Keiles, Sc.D., Associate in Biochemistry; and Harry G. Dav, Sc.D., Associate in Biochemistry; School of Hygiene and Public Health, Johns Hopkins University. Fifth edition. New York: The Macmillan Co., 1939.

A standard reference book for physicians, dietitians and students. The chapters on dietary habits of man in different parts of the world and on deficiency diseases are of particular interest to public health workers.

11. The Foundations of Nutrition. By Mary Swartz Rose, Ph.D., Prof. of Nutrition, Teachers College, Columbia University. Third edition. Price \$3.50, pp. 625. New York: Macmillan Co., 1938.

This text on nutrition is "a gold mine of information . . . one of the best and simplest expositions in the English language."

12. Vitamin B (Thiamin) and Its Use in Medicine. By Robert R. Williams, Sc.D., Bell Telephone Laboratories, and Tom D. Spies, M.D., associate professor of medicine, Univ. of Cincinnati. Price \$5.00, pp. 411. New York: The Macmillan Co., 1938.

Dr. Williams probably has done more than any other person in investigating the properties of Vitamin B, and was awarded the Willard Gibbs Medal of the American Chemical Society. Methods of application of these research findings to actual

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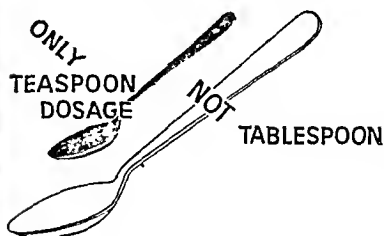
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During the eight years from 1927 to 1935 the Red Cross through its chapters distributed more than 500,000 pounds of pure yeast, and 750,000 packages of garden seeds. Each package was large enough to plant between a quarter and half an acre of garden.

The most important result of this activity has been a drop in the annual pellagra death rate from 7,000 to 3,000 or less. Other incidental results have also been achieved. Thousands of acres were converted into gardens where gardening had become a lost art; canning again became popular and provided protection during winter months. Health departments, physicians and others helped in this drive to free the section of the scourge.

Pure yeast is one of the most potent remedies known for the treatment of pellagra. In proper dosage it will usually cure in six to ten weeks—even without alteration of the usual harmful diet of pork, molasses and meal.

So says Dr. DeKleine, and he should know. The Red Cross continues instruction in nutrition through its many hundred chapters, and continues to promote gardening and the distribution of yeast. To continue and expand work of this kind, the Red Cross is seeking 1,000,000 new members during its annual Roll Call, from Armistice Day to Thanksgiving this year. Membership dues finance all day-to-day work of the Red Cross, and only in time of great disaster are special contributions and gifts called for.

clinical practice make the book invaluable alike to the physician, the biologist and the student of nutrition.

MORE READABLE — LESS TECHNICALLY WRITTEN BOOKS

1. The Normal Diet. Council on Foods, American Medical Association. Price, pp. 16. Chicago: American Medical Association, 1938.

2. Your Diet and Your Health. By Morris Fishbein, M.D., Editor, Journal of the American Medical Association. Price \$2.50, pp. 298. New York: McGraw Hill Book Co., 1937.

In a simple language, interestingly

written, are given the most generally recognized and accepted truths about diet.

3. Man, Bread and Destiny. By C. C. Furnas, Asso. Prof. of Chemical Engineering, Yale University, and S. M. Furnas, formerly instructor in Nutrition, Univ. of Minnesota. Price \$5.00, pp. 364. Baltimore: Williams & Wilkins Co., 1937.

"In the light of the knowledge which we now have on the influence of food on physical and mental fitness, the authors review the course of civilization and show how changes in

food supply have been responsible for the waxing and waning of races and nations. This book does not bring to light any facts new to those who have thoroughly studied the subject; it is a book for the intelligent layman rather than the student. The authors write from a wide knowledge and with a sense of humor which makes the book easy and interesting to read." J. B. Orr.

4. Have You Had Your Vitamins? By Harry N. Holmes, Ph.D. Severance Chemical Lab., Oberlin College. Price \$1.00, pp. 60. New York: Farrer & Rinehart, 1938.

"It is significant that Dr. Holmes, a leader in pure science, who has himself recently made the significant contribution of securing Vitamin A in crystalline condition, has in this little volume endeavored to summarize and briefly interpret for the layman the practical aspects of our vitamin knowledge. An excellent balance has been maintained between the interesting historical developments, our present knowledge, and the practical aspects of vitamin administration." Ind. and Eng. Chem.

5. Food, Nutrition and Health. By E. V. McCollum, Ph.D., Prof. of Biochemistry, and J. Ernestine Becker, M.A. (title) School of Hygiene and Public Health, Johns Hopkins Univ., 4th edition, revised. Price \$1.50, pp. 154. Baltimore: Published by the authors, 1937.

A guide for the application of the science of nutrition to the health of the individual. The subject matter is presented in non-technical style, understandable to the intelligent reader.

6. Facts, Fads and Frauds in Nutrition. By Helen S. Mitchell, Ph.D. and Gladys M. Cook, Mass. State College. Price, free, pp. 32. Amherst, Mass.: Mass. Agric. Expt. Station.

This bulletin has been written for a nutrition-conscious public which has a limited basis for evaluating the merits of claims made in advertising and by the proponents of fads.

7. The Deuce of Reducing. By Katherine Mitchell, Dietitian, Los Angeles County General Hospital. Price \$1.50, pp. 112. New York: Covici Friede, Publishers, 1937.

This book will be read easily because of its witty style, agile and spicy, but keyed to the times. A helpful introduction by Dr. Morris Fishbein supplements Miss Mitchell's warning of the dangers of radical reducing without medical supervision.

8. The Normal Diet and Healthful Living. By W. D. Sansum, M.D., Chief of Staff of Sansum Clinic and Director of Metabolic Research Dept., Cottage Hospital, Santa Barbara, Calif.: R. A. Hare, M.D., Sansum Clinic and Ruth Bowden, B.S., Dietitian Sansum Clinic. Price \$2.00, pp.



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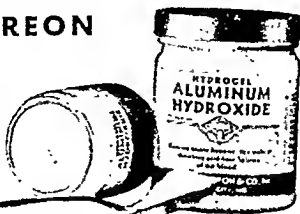
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3. Q. How many calories per ounce of Karo by weight?

A. 90 calories.

4. Q. How many calories per tablespoon of Karo?

A. 60 calories.

5. Q. Is Karo free from pathogenic organisms?

A. Yes, Karo is heated to 165° F. and then poured into pre-heated cans and vapor vacuum-sealed.



Let there be no confusion of issues in ordering the proper carbohydrate. It must be a milk modifier whose virtues are vested in its components rather than in its container. There must be nutritive value, not ornamental appeal. We prefer to extol the virtues of Karo.

The original Syrup, Karo, provides the correct dextrin-maltose-dextrose mixture in a sterile can. The constituents of Karo are nutritionally balanced, chemically dependable and bacteriologically safe.

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Infant feeding practice is primarily the concern of the physician; therefore, Karo for infant feeding is advertised to the Medical Profession exclusively. For further information, write Corn Products Sales Company, Dept. DN 11, 17 Battery Place, New York City, N. Y.

245. New York: The Macmillan Co., 1938.

A concise summary of the type of instructions the authors have been giving their patients for a number of years and which they say "has resulted in good both to patients and authors."

9. Vitamin Chart. Nutrition Service, Division of Maternity, Infancy and Child Hygiene, New York State Department of Health, Albany, N. Y. Single copies are free. 1 sheet 8½" x 11".

10. The A B C of the Vitamins: A Survey in Charts. By Jennie Gregory. Price \$3.00, pp. 93. Baltimore: The Williams and Wilkins Company, 1938.

The story of the vitamins presented by means of charts and graphs in a 9 x 12 inch volume.

RECENTLY PUBLISHED REVIEW ARTICLES

1. Nutrition and the Health of the School Child. Mary Swartz Rose, Ph.D., Teachers College, Columbia Univ., Jour. Amer. Dietetic Asso., 15, 63, Feb., 1939.

2. Present Status of Dental Caries in Relation to Nutrition. Nina Simmonds, Se.D., Univ. of California College of Dentistry. Amer. Jour. Public Health, 28, 1381, Dec., 1938.

3. The Relation of Nutrition to the Development of Sound Teeth. E. N. Todhunter, Ph.D., Asso. Prof. of

Nutrition, State College of Washington. Jour. of Home Econ., 30, 93, Feb., 1938.

4. The More Abundant Diet. James S. McLester, M.D., The Univ. of Alabama. Jour. Amer. Dietetic Asso., 14, 1, Jan., 1938.

5. Recent Advances in Nutritional Research. E. V. McCollum, Ph.D. Johns Hopkins Univ. Jour. Amer. Dietetic Asso., 14, 8, Jan., 1938.

6. Nutritional Deficiency. George E. Minot, M.D., Harvard Univ. Med. School. Annals of Internal Medicine, 12, 429, Oct., 1938.

7. Diseases of Metabolism and Nutrition. Review of Recent Contributions. Dwight L. Wilbur, M.D., Univ. of Calif. Published each year in March issue Archives of Internal Medicine.

For Painful Rheumatic Affections

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A Combined Effect

"The salicylates—are useful for their analgesic properties. If used, they may be combined with the iodides in one mixture¹."

"In acute cases (arthritis) with pain and swelling, salicylates and iodides were used²."

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New and Non-Official Remedies³ confirms the value of associated alkali therapy as follows: "In practice these compounds (of salicylic acid) are not superior to sodium salicylate, which does not produce direct gastric irritation when properly guarded by a bicarbonate."

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1. Copeman, W.S.C.: The Medical Standard, "Some Principles in the Modern Treatment of Rheumatic Diseases," p. 12, May, 1930. 2. Illinois Medical Journal, September, 1930, p. 2231. 3. New and Non-Official Remedies, pub. by Amer. Med. Assoc., p. 370, 1934.

Write for samples and literature

EFFERVESCENT PRODUCTS, Inc.

ELKHART.

INDIANA

SHORT-WAVE ULTRA-VIOLET RADIATION

Germ-killing radiation from short-wave ultra-violet tubes is the dairy industry's latest answer to the problem of sanitary control of milk-bottling and distribution.

Constituting the first practical large-scale application to inorganic materials of General Electric's recently-introduced germicidal lamps, the new sanitary control method was demonstrated here this afternoon to state health officials and dairy industry leaders by R. J. Alden, Sanitation Engineer of the Cowdrey Products Company, manufacturers of milk bottle hood-caps and machinery for the dairy industry.

Employing twenty-one of the new germicidal lamps, the installation continuously irradiates the hood-caps from the moment the paper is unrolled until the finish of the manufacturing process, when the hood-caps are inserted into sealed containers.

Rigid tests of the new method, conducted during the last three months under the supervision of John B. Enright, milk Bacteriologist of the City of Fitchburg, show that it reduces the bacteria-colony count on the hood-caps applied to the pouring-lips of milk bottles—a major focal point of infection—from the commonly accepted limit of 500 bacteria-colonies to an average of less than ten.

It was revealed by Mr. Alden that the new germicidal irradiation process was recently described to Lester T. Tompkins, Director of the Division of Dairying and Secretary of the Milk Regulation Board of the Commonwealth of Massachusetts, in the presence of Governor Leverett Saltonstall and William Casey, State Commissioner of Agriculture, who has jurisdiction over all regulations pertaining to the production and distribution of milk. In a releasable written communication to the Cowdrey company, following the meeting, Mr.



C-C4

Miss G: Always constipated, sad and in part to the cellular bad breath, has the fiber and pectin popular nostrils to the intestinal residues, the property of absorbing the fiber is a further spastic constipation

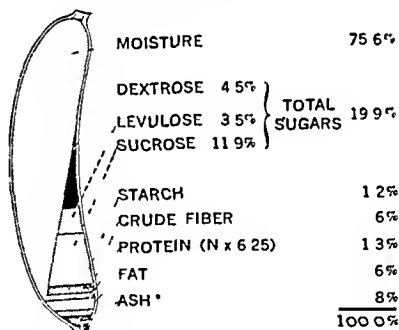
A SLUGGISH COLIC of the banana is to be parent medicine. Points stand out as qualifying chance to help it. It is rewarded in a manner of diets. These are summarized

Nevertheless, the reaction associated with it is rewarded in a manner have the natural assistance

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- Intestinal Disturbance
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- Convalescent Diets

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		Calories	Protein	Calories	Protein	Calories	Protein	Calories	Protein	Calories	Protein	Calories	Protein
Cereal		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Vegetables		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Fruit		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Eggs		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Meat		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Fat		100	1.0	100	1.0	100	1.0	100	1.0	100	1.0	100	1.0
Total		500	5.0	500	5.0	500	5.0	500	5.0	500	5.0	500	5.0

o This analysis card shows the estimated approximate minimal and optimal requirements of infants, a chemical analysis of Gerber's Baby Foods and the average food values of foods included in the infant dietary. The information was compiled from research by Gerber's dietetic staff in conjunction with the Research Fellowship established by Gerber's at Michigan State College.

The doctor will find it useful and reliable in working out infant diets. Note particularly the excellent values in iron in the dry cereal and the good values in all of the canned strained foods—also the fact that both peas and spinach are good supplementary sources of Vitamin C.

An additional analysis card on Gerber's Cereal Food will also be received by those sending the coupon below.

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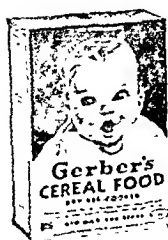
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NEW LABORATORY

Establishment of a new laboratory for the study of filterable virus diseases, in the treatment and prevention of which science is believed to be at the threshold of an important advance, is announced by the Squibb Biological Laboratories.

Dr. Raymond C. Parker, biologist of the Rockefeller Institute for Medical Research, and for many years an associate of Dr. Alexis Carrel, has been appointed to head the laboratory, which will operate as a unit of the Biological Division of E. R. Squibb and Sons at New Brunswick, N. J. The new building is a continuation of a program of expansion which began in the Fall of 1938 with the dedication to pure science of the \$750,000 laboratory of the Squibb Institute for Medical Research.

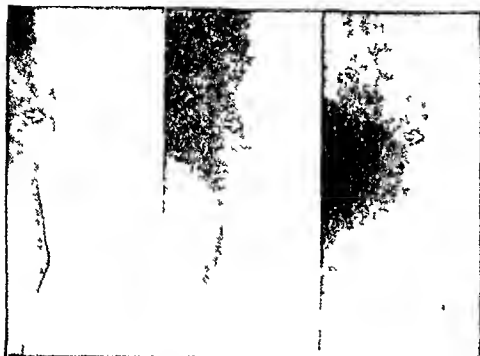
"Enlargement of the company's biological facilities was undertaken because rapid development in the knowledge of filterable viruses has made it probable that our ability to prevent and control infection from these sources will have a rapid expansion in the immediate future. Dr. John F. Anderson, director of the Biological Laboratories, explained.

Among the common diseases caused by filterable viruses, Dr. Anderson pointed out, are smallpox, rabies, equine encephalitis, measles, chicken pox, poliomyelitis, and the common cold. No specific product for the prevention of four of these diseases—the common cold poliomyelitis, chicken pox and measles—is now available.

More than 500 scientists from ten nations witnessed the first demonstration of the new virus laboratory during a tour of the Squibb Institute and the Biological Laboratories on September 6 and 7. The group, composed of delegates to the Third International Congress for Microbiology, which met in New York City, September 2 to 9, also inspected the Rockefeller Institute for Medical Re-

Prompt Symptomatic Relief in PEPTIC ULCER

...with **PLAIN KNOX
GELATINE (U. S. P.)**



CASE I—FEMALE, 74

Uncomplicated gastric ulcer first demonstrated by Roentgen rays in 1934. Diet and alkalies afforded little relief. Accompanied by loss of weight. Repeated X-ray studies in 1936 and 1937 showed no improvement. She was placed on a diet-gelatine regime in November, 1937. Relief immediate. Gained weight. Roentgen studies in April, 1938 showed no demonstrable ulcer.

NOTE:

The gelatine used in this study was plain Knox Gelatine (U.S.P.) which assays 85% protein and which should not be confused either with inferior grades of gelatine or with sugar-laden dessert powders, for these latter products will not achieve the desired effects. When you desire pure U.S.P. Gelatine, be sure to specify KNOX. Your hospital can get it on order.

CLINICAL research has recently demonstrated the effectiveness of utilizing plain Knox Gelatine (U.S.P.) in treatment of peptic ulcer. In a group of 40 patients studied, 36 (or 90%) were symptomatically improved; 28 of these (or 70%) experienced *immediate relief of all symptoms*. Other than dietary regulation which included frequent feedings of plain Knox Gelatine no medication was given except an occasional cathartic.

NO DANGER OF ALKALOSIS

This regime thus eliminates the "alkalosis hazard" attendant upon continued alkali therapy. In discussing the mode of action by which gelatine brings peptic ulcer relief, Windwer and Matzner* speak of the acid-binding properties by which proteins can neutralize acids, and they state that the frequent gelatine feedings "apparently caused more prolonged neutralization of the gastric juice."

PEPTIC ULCER FORMULA

Empty one envelope Knox Gelatine in a glass three-quarters filled with cold water or milk. Let the liquid absorb the gelatine. Then stir briskly and drink immediately before it thickens. Take hourly between feedings for seven doses a day.

*Windwer and Matzner, *Am. Jl. Dig. Dis.* 5:743, 1939.

WRITE DEPT. 475



KNOX GELATINE LABORATORIES

JOHNSTOWN

NEW YORK

Please send complete details of the Knox Gelatine peptic ulcer regime.

Name _____
Address _____
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search at Princeton on Wednesday, September 6.

The program at New Brunswick will be divided into two sections, exhibitions and charts illustrating new developments in the Squibb Institute, and a display of biological products developed by large scale methods in the Biological Laboratories. German, Spanish, French and Italian interpreters will be provided for those who do not speak English. Stables in which 200 horses and 1500 rabbits are maintained for the production of antitoxic and antibacterial sera will be shown to the foreign microbiologists.

The new virus laboratory is housed in a specially constructed building,

and is equipped for work with chick embryos and tissue culture, two of the techniques for work in this field. The actual working quarters consist of a large general laboratory equipped with every facility for chemical and histological work, a general preparation room for washing, drying, packing and storing the various materials that are used, two special culture and operating rooms provided with filtered ventilation, a spacious incubator room, an animal preparation room, a bleeding room and ample animal quarters.

The arrangement of the rooms is such that the air of the culture suite proper is protected at all times from

the air of the general laboratory and office quarters on the one side, and of the animal room on the other. It is also possible for visitors to observe every step of the work in progress without entering any of the various rooms of the culture suite.

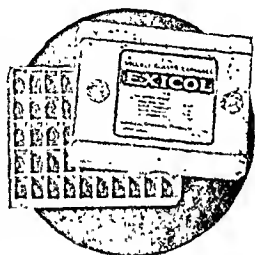
The program of the visiting scientists at New Brunswick includes a demonstration of the Institute's work on the effects of Vitamin K and some of the new simple synthetic products which have an effect similar to that of the natural vitamin. A test, using baby chicks and allowing Vitamin K to be assayed in six hours, will be carried out. Charts will show the relationship of Vitamin K deficiency to blood clotting, a comparison of methods of assay of Vitamin K, and the isolation of the natural vitamin from alfalfa. Natural and synthetic products with Vitamin K activity will be displayed.

Dr. Parker was born in Newport, Nova Scotia, on October 18, 1903. He received the degree of Bachelor of Arts from Acadia University in 1924, and the degree of Doctor of Philosophy in 1927 from Yale University, where he was Sterling Fellow, and assistant in zoology. From 1927 to 1929 he studied in Germany as National Research Council Fellow in biology. He became assistant in the division of experimental surgery at the Rockefeller Institute in 1930, and associate in 1935. His researches have dealt with selection in protozoa and the biology of tissue cells in pure cultures. Dr. Parker is the author of the leading text on "Methods of Tissue Culture."

WOLDMAN, EDWARD E. AND POLAN, CHARLES G.

Am. J. Med. Sci., Cleveland, Ohio, p. 155, Aug., 1939.

The continuous drip method of using colloidal aluminum hydroxide has been in use three years; it is especially designed to neutralize gastric acidity uninterruptedly and thereby allow peptic ulcer to heal. The purpose is the same as most of other forms of treatment for ulcer but as Crohn and Reiss have shown magnesium oxide and sodium bicarbonate are the most powerful excitants of gastric secretion, excepting histamine. Colloidal aluminum hydroxide is mildly astringent and non-irritating. It is amphoteric, with a pH of 6.9; and does not cause alkalosis. It contains about 5% of aluminum hydroxide and about 0.6% of sodium chloride in water. It combines with 12 times its volume of tenth-normal hydrochloric acid within half an hour. It is not absorbed from the gastrointestinal tract, as shown by Ivy, in dogs and by Einsel, Adams and Myers, in man. It coats the ulcer with a jelly-like mass. It is helpful in



EXICOL

(Oleic Acid and Bile Salts)

Merits Your Serious Consideration Because . . .

1. It is a potent and proven cholagogue—stimulating both bile secretion and gall bladder emptying.
2. The clinical results obtained with Exicol tend to prove the correctness of the physiologic principles upon which this theory is based.
3. It is a rational and dependable adjunct in the therapy of non-surgical diseases of the biliary tract.
4. Exicol therapy makes feeding of high fat diets unnecessary.

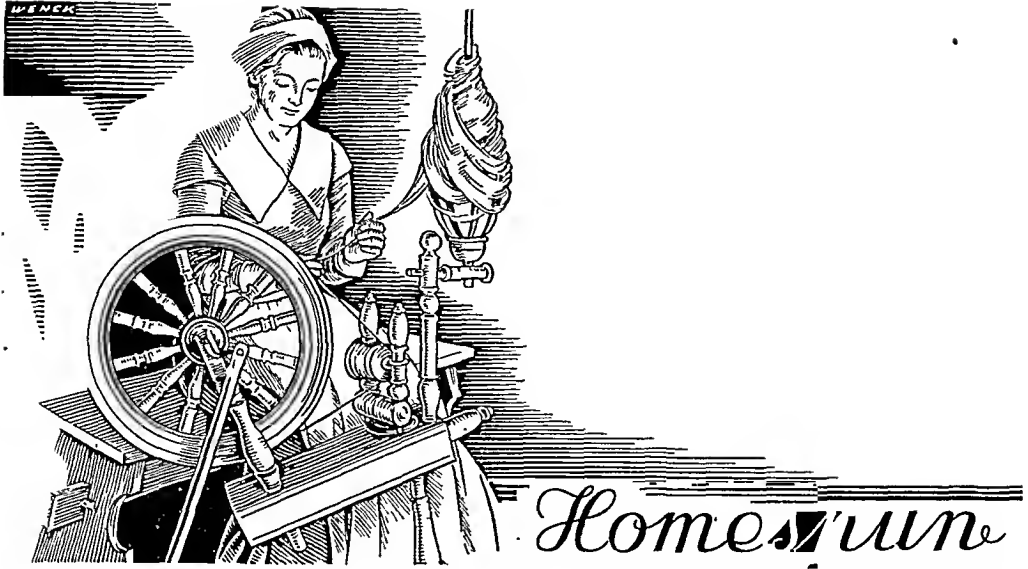
Exicol is indicated in the treatment of chronic cholecystitis, chronic cholangitis, toxic hepatitis and functional biliary insufficiency.

Dosage: Two capsules three times daily before meals.

Supplied in boxes of 36 and 100 capsules.

Literature on Request

Brooklyn Scientific Products Co. Inc.
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Cloth and Home-Brewed "Remedies"

Homespun cloth still has its quality appeal but home-brewed remedies are done with. Advanced methods in the art of pharmacy have replaced the rule-of-thumb of the kitchen chemist.

An impressive example of modern exacting compounding is Loraga, in which so fine an emulsification of mineral oil and agar is attained that thorough mixing with the intestinal contents is assured and leakage obviated. A pleasing taste is achieved without artificial flavoring. Absence of sugar, alcohol and alkali in Loraga makes it suitable for all age periods.

Loraga contains no added laxative ingredients. A fine mineral oil emulsion, indeed, in the treatment of the costiveness of children and adults when no active peristaltic stimulation is indicated. You can obtain a trial supply of Loraga by writing for it on your letterhead.

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A WILLIAM R. WARNER PRODUCT

SUPPLIED IN 16-OUNCE BOTTLES

WILLIAM R. WARNER & CO., INC., 113 West 18th Street, New York City

arresting hemorrhage. The drip must be continued throughout the night and not more than one hour should elapse without medication. In the healing of an ulcer the granulation is extremely friable and must be protected until the crater is filled in, which requires 7 to 10 days. The method has been used successfully in bleeding ulcers as it promotes clot formation and then protects the delicate fibrin from the action of the unbuffered gastric juice, and pepsin is not active in alkaline or neutral solutions.

The treatment requires hospitalization of the patient. The colloidal aluminum hydroxide diluted to 25% is instilled into the stomach through

a naso-gastric collapsible thin rubber tube, $\frac{1}{4}$ inch in diameter, passed with the aid of silkworm-gut suture which is left in place. The tube is passed only as far as the lower end of the esophagus. In the cases in which the tube was not used one ounce of the solution was given every hour during the day and every 2 hours during the night. Usually a sedative was given in the evening. The food consists of small quantities of a bland diet every two hours for twelve hours, milk with one-third cream, cooked cereals (oatmeal, farina, cream of wheat), a soft boiled egg, a slice of toast, butter, cream soups, gelatin, custard, tapioca and junket. For constipation mineral

oil is given daily or enemas every other day. The treatment is employed in cases of hematemesis and melena excepting that the naso-gastric tube is not passed until vomiting ceases but the colloidal aluminum hydroxide is given by the mouth meanwhile and the same diet and sodium phenobarbital hypodermically as a sedative. Small transfusions, 250 cc. are given when the systolic blood pressure is less than 90 and hgb. below 30%.

In three years 407 patients with peptic ulcer were treated with colloidal aluminum hydroxide. There were 322 men and 85 women. The drip method was employed in 270 patients and 86 were on oral treatment. Of these 101 were bleeding on entering the hospital. Twenty-two patients had both gastric and duodenal ulcers, nine had marginal ulcers, six after gastro-enterostomy and three after gastric resection. The most striking features of the treatment are: 1, the prompt relief of pain, 2, the rapid healing of the ulcer, 3, the healing of refractory ulcer, and 4, the excellent results in case of massive hemorrhage, the mortality in the cases being only 3% as compared with 29% in 38 cases in the same hospital in the five year period preceding the inauguration of this form of medical treatment.

Allen Jones, Buffalo.

BENDICK, ARTHUR J.

Early Esophageal Carcinoma.
Am. J. Roent. and Radium
Therapy, Vol. XLI, 603, 1939.

Bendick reports a case of early carcinoma of the esophagus. The importance of this case is that there were only slight burning pains, whenever the patient swallowed hot or cold liquids. The well known symptoms of difficulty in swallowing, bleeding or loss of weight were not present. The routine roentgenographic examination was entirely negative.

Bendick stresses the importance of the examination of the patient in recumbent position. Only in this position the presence of the growth of 1.5 cm. in diameter could be visualized.

Franz J. Lust, New York, N. Y.

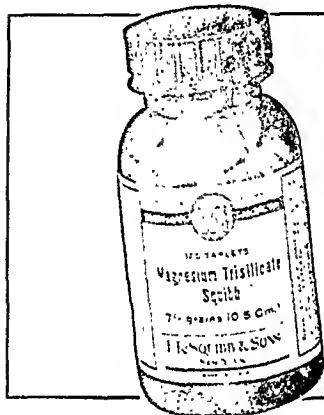
EINHORN, MAX.

The Value of the String Test for the Diagnosis of Peptic Ulcers.
Gastro-enterologia, Vol. 64, p. 65-67, June, 1939.

The string test which was introduced 30 years ago by Einhorn is especially valuable in cases with shallow lesions in the stomach or duodenum, in which a deformity of the stomach or duodenal wall is not present.

Einhorn reports cases of peptic ulcer in which the roentgenological examination of the gastro-intestinal

Antacid of choice in Gastric Hyperacidity



MAGNESIUM TRISILICATE SQUIBB

RECENTLY magnesium trisilicate was proposed for the treatment of peptic ulcers because its sustained antacid and adsorptive effects provide an environment conducive to healing.

Referring to magnesium trisilicate, Mutch¹ (Guy's Hospital, London) states: "Its antacid power is sustained for hours even in the presence of an excess of acid. Not only does this facilitate the continuous control of hyperchlorhydria in the gastric contents as a whole, but it furnishes a basis for a local antacid therapy in the floor of the ulcer itself. In the presence of acid the trisilicate acquires a gelatinous consistency, and if any of the mass lodges in the ulcer crater, it will

¹Mutch, N.: *Brit. M. J.* 1:143, 205, 254, 1936.

progressively neutralize the acid which diffuses through it."

Magnesium trisilicate does not reduce the gastric reaction below the neutral point, nor is it absorbed. Hence there is no possibility of its inducing an alkalosis. Since the general motility of the digestive tract is not disturbed, it does not cause constipation or diarrhea. These features make magnesium trisilicate an antacid of choice in gastric hyperacidity.

Magnesium Trisilicate Squibb is supplied as $7\frac{1}{2}$ gr. palatable, slightly flavored (peppermint) tablets in bottles of 100 and 1000.

Total daily dosage varies between 6 and 24 tablets according to the patient's condition and response.

For literature address the Professional Service
Department, 745 Fifth Ave., New York, N. Y.

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MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

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....QUITE CONTRARY

TODAY when a child is contrary, nervous, irritable and hard to manage the physician seeks a definite reason. That reason may be dietetic . . . a slight deficiency of some of the vital elements which the growing body needs. Physicians, Nurses and Dietitians well recognize the need for balanced dietaries, and more and more of them are recommending COCOMALT.

COCOMALT HAS "DOUBLE VALUE" . . .

When this malted food dietonic is added to milk the food value is materially increased. The child enjoys the rich full flavor; and COCOMALT acts as an incentive to milk drinking. COCOMALT contains calcium . . . phosphorus, iron . . . Vitamins A, B₁, D and G . . . provides quick energy . . . body building nutrients.

VARIED USES OF COCOMALT

- Infant Feedings
- Febrile Diseases
- Post and Pre-Operative Regimes
- Peptic Ulcer Diets
- Bland Diets
- Pregnancy and Lactation
- Convalescence
- Anorexia
- Growing Child



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THE MALTED FOOD DIETONIC

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OFFER**



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Please send me the new Dietetic Manual—"A Modern View of Adequate Diet," together with a sample of COCOMALT.

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City _____ State _____ Dept. 1J 11 _____

tract gave no evidence of any lesion. The string test, however, enabled the author to make the diagnosis and proved again to be very valuable.

Franz J. Lust, New York, N. Y.

CUNHA, FELIX.

The Duodenal Syndrome Associated with Aberrant Superior Mesenteric Artery. J. of the Inter. College of Surgeons, Vol. 2, 93, 1939.

Cunha describes the syndrome which is due to an aberrant mesenteric artery. The clinical signs are those of a duodenal ulcer. However, the gastric contents is normal, the

roentgenological examination shows no sign of a peptic ulcer either in the stomach or in the duodenum. Cunha stresses the fact that fluoroscopy however is the most important examination. Roentgenograms cannot possibly demonstrate the condition unless extreme dilatation of the duodenum has taken place. Fluoroscopy reveals the presence of antiperistalsis in the second and third portion of the duodenum, the barium reaching the point of compression at about the terminus of the latter, then being unable to follow through, antiperistaltic waves of muscular action carry it backward to the pylorus, with the production of

an endless churning back and forth between these two points. After some time a secondary dilatation of the duodenum takes place. In those cases in which the syndrome has been present over a long period, absolute stasis in the duodenum is sometimes noted, brought about through fatigue inertia of the smooth muscle. Marked changes in body weight, gross fat depletion or gross fat increase, alter the anatomic relationship and therefore the mechanical function of that region of the duodenum and are apparently an etiologic factor in the occurrence of the described symptom.

Franz J. Lust, New York, N. Y.

GERSTER, JOHN C. A.

Retroperitoneal Chyle Cysts. Annals of Surgery, Vol. 110, No. 3, pp. 389-410, Sept., 1939.

Gerster reports a case of retroperitoneal chyle cyst. The clinical findings were those of a tumor in the right epigastrium. Intensive roentgenological studies enabled the diagnosis of a retroperitoneal tumor pressing on the rear wall of the second part of the duodenum and on the gall bladder. At the operation the tumor was found attached to the anterior aspects of bodies of first and second lumbar vertebrae between the aorta and the inferior vena cava. The aorta was entirely free, but the inferior vena cava was intimately adherent to the right side of the tumor for a distance of three inches. The contents of the tumor was a milky fluid. This tumor was due to a trauma.

Gerster emphasizes that the exact diagnosis is determined by the microscopic character of the cyst wall (lymphangioma, dermoid, hydronephrosis). Analysis of the fluid contents is of secondary interest.

Many cases of chyle cysts are reported under different headings. Gerster's compilation of the literature should be well appreciated.

Franz J. Lust, New York, N. Y.

JUNGNER, G., RYDIN A. AND JOSEPHSON, B.

Elimination of Cholic Acids. II. In Experimental Jaundice. Acta Med. Scand., 97(3/4):254-264, 1938.

The surface adsorption of cholates on the walls of the blood vessels does not occur in obstructive jaundice. The blood cholic acid in animals with toxic hepatitis (after P or CCl₄) was greater than normal but less than that seen in obstructive jaundice, and there is a greater delay in excretion due to injury to the liver parenchyma. Estimation of the blood cholate concentration after injection of Na cholate should therefore furnish a diagnostic liver function test.—J. F. W. (courtesy of Biological Abstracts).

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THE effective answer to the problem of constipation—where irritation or roughage are contraindicated—is the hydrogel, Serutan. Through its unique ingredients, Serutan has a swelling power equal to ten times its own weight. It provides a bland, non-oily, gelatinous bulk to the fecal mass that induces an effective colonic reflex, insuring copious, normal stool elimination.

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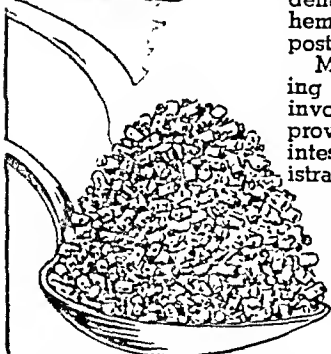
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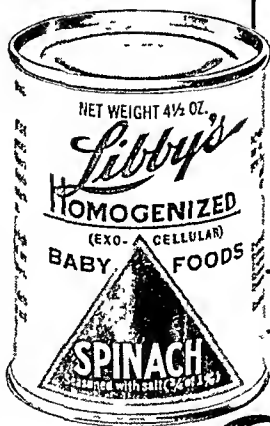


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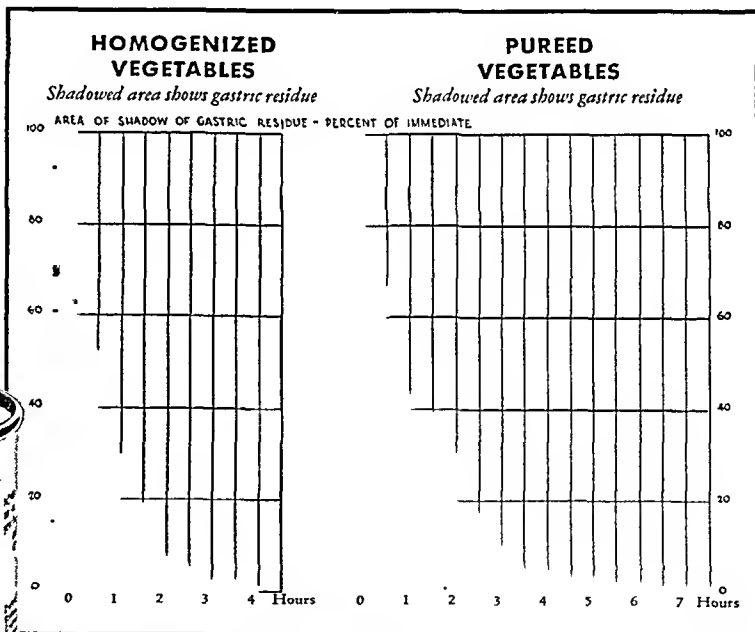
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who would like to
supplement a bland diet
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THESE CHARTS TELL A SIGNIFICANT STORY

These two charts compare the rates of digestion of homogenized vegetables and pureed vegetables in the stomachs of 8 patients with chronic peptic ulcers. The gastric evacuation time proved to be significantly less for homogenized vegetables (an average of 3.5 hours) than it was for pureed vegetables (an average of more than 5.0 hours).



NOTE: It often seems desirable to add vegetable supplements to the bland diets of patients with functional disturbances of the gastro-intestinal tract—in order to maintain adequate nutrition. At the same time it is essential that the stomach be given both motor and secretory rest. The easy digestibility of specially homogenized vegetables suggested that, in these cases, homogenized vegetables have unusual advantages. To investigate their possibilities, a series of experiments was undertaken. The charts reproduced on this page summarize one phase of these experiments. For a full summary of these experiments (reported in September issue of The Journal Lancet) write Libby, McNeill & Libby Research Laboratories, Dept. AD-11, Chicago.



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3 Vegetable Combinations
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While KONSYL, the original concentrated vegetable muciloid made from *Plantago Ovata*, is indicated in chronic constipation it is also of value in the treatment of the following conditions:

1. *In catarrhal colitis* caused by purgatives, nervous spasm of the bowel and in chronic irritation caused by coarse indigestible foods, Kongsyl by forming a soft bland non-irritating bulk will usually have a beneficial effect.

2. *Headaches.* There are many cases of headache, lethargy and dizziness that are due to colonic stasis, or clogging of the large bowel with fecal material. Kongsyl, by establishing regular elimination, is usually of great benefit in these cases.

3. *Looseness of the bowels.* There are many cases of looseness of the bowel, especially of nervous origin, where Kongsyl by supplying a soft bulk absorbs excessive intestinal fluids and changes loose movements into soft or even formed stools.

Write for clinical test sample and literature.

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AJ 11-39

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A Teaspoonful
makes a
Tumblerful
of "Jelly"



PALMER, WALTER LINCOLN.

*Benign and Malignant Gastric
Ulcers: Their Relation and
Clinical Differentiation.* Ann.
Int. Med., Vol. 13, No. 2, pp. 317-
338, Aug., 1939.

Palmer describes a case of a carcinomatous ulcer of the lesser curvature of the stomach. The roentgenological examination showed it to be a benign lesion. The gastroscopic examination, however, revealed the presence of a carcinomatous ulcer. The histological findings are very well illustrated by the microphotographs. These microphotographs reveal a minute carcinomatous lesion in a fold of the fundus of the stomach. The difficulty of differentiating between benign ulcers and carcinomatous ulcers is emphasized especially in ulcers which show a carcinomatous degeneration. Free acidity of 106 showed after a histamine test. Stool examinations for occult blood varied from negative to strongly positive. Roentgenological examination showed a small gastric lesion. The autopsy showed massive carcinoma metastases to the skeleton. Minute carcinoma metastases to lymph nodes, spleen, and lung.

Franz J. Lust, New York, N. Y.

SCHATZKI, RICHARD.

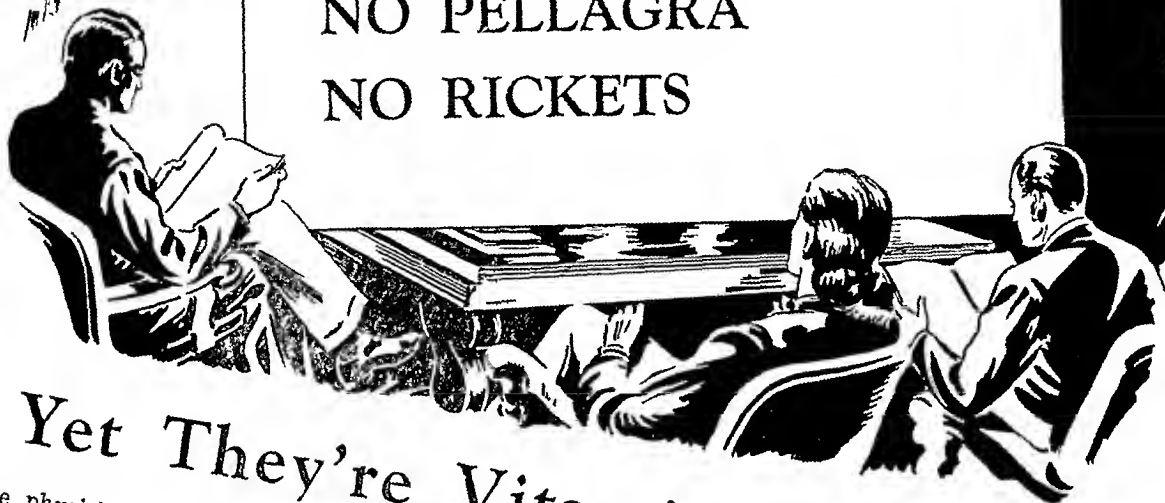
*The Roentgenologic Appearance
of Intussuscepted Tumors of the
Colon.* Am. J. Roent. and Rad.
Ther., Vol. XLI, 4, 549-563, 1939.

Schatzki reports eleven cases of intussuscepted tumors of the colon in adults. It is interesting that three of these were pedunculated submucous lipomas, which showed partial necrosis and ulceration. The rest of his cases was due to carcinomata. Schatzki uses mostly the contrast enema and the flat plate. Oral administration of barium is only an additional method.

The author discusses the roentgenological signs which differ according to the amount of obstruction and intussusception present. The signs are easily explained by the anatomical process. The barium may enter the central canal as well as the peripheral sheath of the colon. Besides, on the flat film a sausage-shaped, homogeneous shadow (representing the intussuscepted portion of the intestine) can be seen. This area may be surrounded by the air-filled sheath. Occasionally even the tumor can be seen heading the invaginated colon. To differentiate between the fecal matter and intussusception, Schatzki stresses the homogeneity of the pathological shadow, whereas fecal matter has a mottled appearance.

As differential diagnosis we have only to consider (1) the inverted cecum and (2) Kantor's string sign

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NO BERIBERI
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NO RICKETS



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Bottles of 5 cc. and 25 cc., with droppers.

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Clinical tests show that many chronic cases of constipation respond to this new treatment — cases in which other forms of treatment were unsuccessful. Prominent clinicians are now prescribing Lactys in certain cases of arthritis. The simplicity and convenience of the compressed 10 gram doses of Lactys are obvious.

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Lactys

For Lasting Results

of regional ileitis. As to the site, Schatzki differentiates between cecocolic (ileocolic) and colocolic intussusceptions. According to the location only slight differences in the roentgenological aspect take place.

Franz J. Lust, New York, N. Y.

SCHENKEN, JOHN R., STASNEY, JOSEPH AND HALL, W. KNOWLTON.

Lack of Antiaemic Principle in Human Liver from Case of Carcinoma of Stomach. Proc. Soc. Exp. Biol. and Med., 40(1): 89-90, 1939.

The injection of an extract prepared from a human liver obtained at necropsy from a patient with carcinoma of the stomach produced no reticulocytic response in a patient with Addisonian pernicious anemia in relapse. The injection of a control extract prepared from the liver of a patient with cerebral hemorrhage caused a marked stimulation of hemtopoiesis. The pyloric and prepyloric portions of gastric mucosa which were replaced by neoplastic tissue in the patient with carcinoma of the stomach have been shown by experimental observations to be most active in the production of the intrinsic factor. — Authors (courtesy of Biological Abstracts).

UPHAM, ROY AND SPINDLER, FRANK.

Studies on Humans with a New Secretagogue Meal. Rev. Gastro-ent., 6(1):12-21, 1939.

The method is too involved for routine gastric analysis. The basis of the test meal is Lumco meat extract with phenol red indicator. The concentration of phenol red in the test meal is compared with that in the extracted samples. It is claimed that the meal gives "absolute figures" for the amount of HCl produced by the stomach. — G. H. C. (courtesy of Biological Abstracts).

REINERS, HERMANN.

Die Harnstoffbildung in der überlebenden, experimentell geschädigten Leber. Arch. Exp. Path. u. Pharmacol., 190:452-460, 1938.

The formation of urea by the surviving cat liver, removed after poisoning of the entire animal with P, and artificially perfused with blood, was unaltered despite severe changes in the epithelial portion of the liver. Damaging the endothelial system of the liver with India ink or electrocopper neither checked nor increased urea formation. Simultaneous acute injury to both tissue systems caused a considerable checking of urea formation, even though changes in each system were not as great as had occurred in the injuries of the single systems as studies. Urea formation

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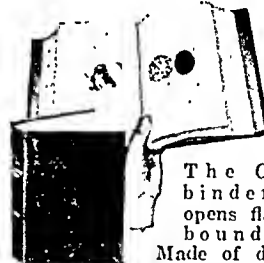
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Dose: One to two teaspoonfuls, followed by copious water.

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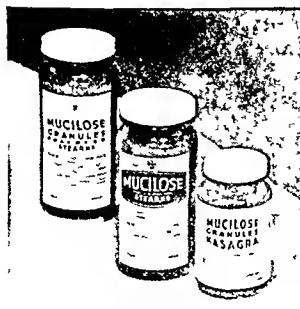
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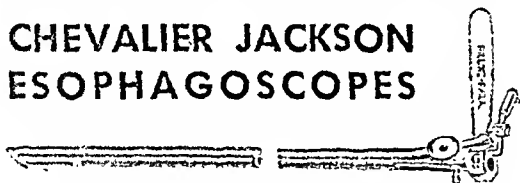
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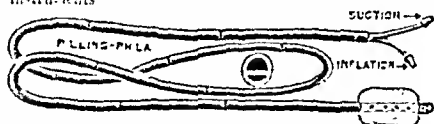
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"Double Barreled Gastro-Enterostomy Tube (Abbott-Rawson) P214S is designed for the post-operative care of malnourished patients subjected to any form of operative procedure anastomosing the stomach to the small intestine.

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is not alone a function of the pithial cells or of the Kupfer star cells; it should rather be considered as a combination work of both tissues. Both the origin and the nature of the injury to the organ are of importance as regards the effects upon this essential function of the liver in diffuse liver pathologies.—C. S. L. (courtesy Biol. Abst.).

STIEBELING, HAZEL K. AND PHIPARD, ESTHER F.

Diets of Families of Employed Wage Earners and Clerical Workers in Cities. U. S. Dept. Agric. Circ., 507, 1-40, 9 figs., 1938.

This analysis of the quantities of different foods purchased, their cost and their nutritive adequacy, in a relatively well-to-do population group, is based on about 4,000 weekly records, obtained from December, 1934, to February, 1937, in 43 industrial centers in 8 major geographical regions of the U. S. Most of the families were whites; some were Negroes in Middle Atlantic and Southern cities. Median expenditures (whites) ranged from \$2.10 a person a week. (East South Central) to \$2.85 (Pacific coast); of Negroes, \$1.55 (Southern) to \$2.40 (middle Atlantic). Expenditures for food rose with increased economic well-being. Such increments were most pronounced in milk, butter, cream, eggs, meat, fruits, and succulent vegetables, and least for grain products, sugars, and fats other than butter and cream. The average consumption of 36 important groups of foods is given by level of food expenditure and by season, and for 4 regions 194 individual food items are also presented. Comparisons of the average nutritive values of the diets (calories, protein, Cn, P, Fe, vitamin. A value, Vitamin B₁, ascorbic acid (Vitamin C), riboflavin, and the pellagra preventive factor) with suggested daily allowances for each unit are made. The middle 50% of the white families received per requirement unit per day 70-95 gms. of protein; 0.50-0.83 gm. of Ca; 14-17 mgms. Fe; 2,000-4,500 I. U. of Vitamin A; 400-600 I. U. of Vitamin B₁; 50-100 mgms. of ascorbic acid; and 550-900 Sherman units of riboflavin. From 40 to 60% of the diets of white families were in need of improvement, and over 60% of these of Negro families. Most of the diets derived a relatively high proportion of their calories from the flavorful fats, sugars, meat, poultry and fish, a low proportion from milk products, fruits and vegetables other than potatoes. The white families spent from 1/4-1/2 of their food money for eggs, lean meat, poultry and fish; 1/5-1/4 for vegetables and fruits; but only 1/4-1/5 for milk and cheese. For the Negro families the respective figures were 1/5-1/4 and 1/5. Even the good diets fell short of the optimal allowances of protective foods. More emphasis should be put on leafy and green-colored vegetables and upon milk, many of whose inexpensive varieties and forms yield excellent food value for their cost.—Authors (courtesy of Biol. Abst.).

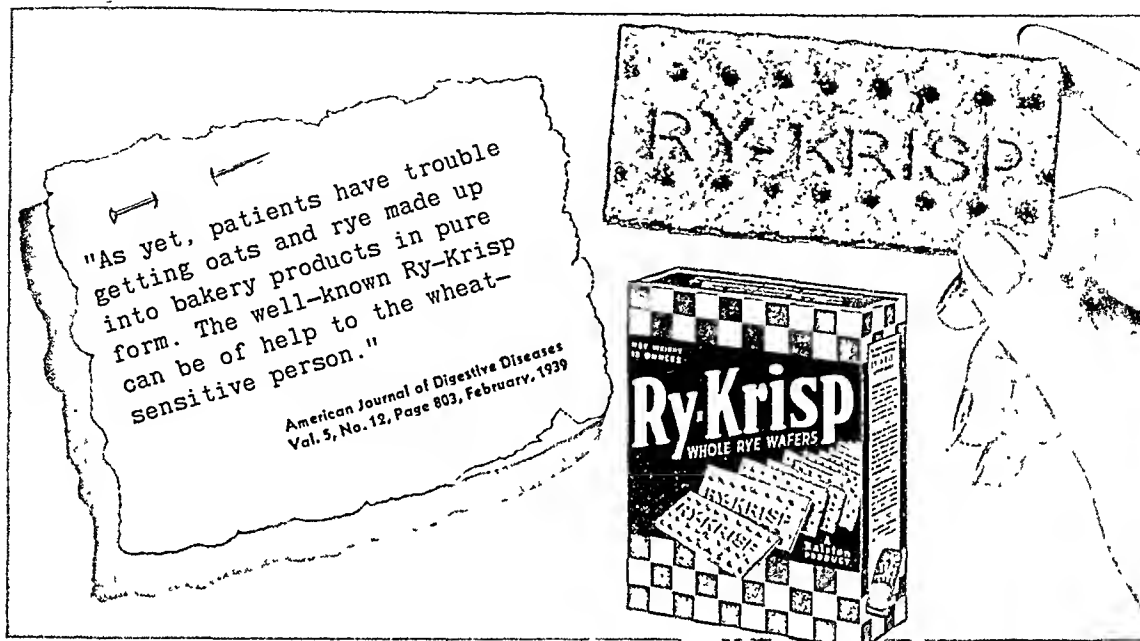
FRUTON, JOSEPH S. AND BERGMANN, MAX.

The Specificity of Pepsin. J. Biol. Chem., 127(3): 627-641, 1939.

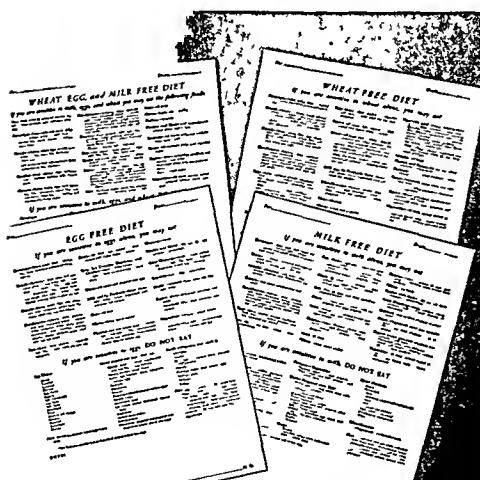
Several specific substrates for crystalline swine pepsin were synthesized—such as carbobenzoxy-L-glutamyl-L-tyrosine and glycyl-L-glutamyl-tyrosine. Carbobenzoxy-L-glutamyl-L-tyrosine was split optimally by pepsin at pH 4 into carbobenzoxy-L-glutamic acid and L-tyrosine. Substitution of the free carboxyls in the substrates inhibited pepsin action. Pepsin, an acid enzyme, therefore required an acidic substrate for its action. The classification of protein-splitting enzymes on the basis of pH optima should be abandoned in favor of a classification on the basis of specificity phenomena. The availability of synthetic substrates for pepsin having only one sensitive peptide bond permits a more precise study to be made of the kinetics of peptic hydrolysis and the quantitative estimation of pepsin in biological fluids. It also permits a comparative study of the relative specificities of pepsins of various animal spp.—Authors (courtesy Biol. Abst.).

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3. Ry-Krisp is readily available at most grocery stores and food markets all over America.

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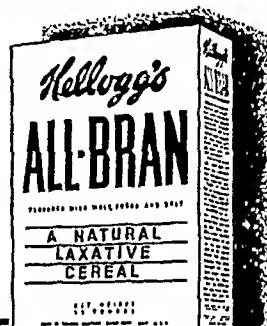
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—a natural laxative cereal
—is confidently recommended
for cases of constipation
resulting from lack of bulk
in the diet

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**AS ONE PHYSICIAN TO ANOTHER. . .
WHAT IS THE CAUSE OF CONSTIPATION?**



Obviously, there is no single cause. Each case must be judged on its own merits. Anatomical differences, variations in diet and habit and specific pathological entities all enter into the cause. However, it is safe to say that faulty habit plays a role in the great majority of cases, and that loss of neuro-muscular tone is a very common secondary factor.

To make habit training easier, a bland, pure mineral oil is important. To increase tone of debilitated intestinal musculature and nervous system caused by Vitamin B-1 deficiency, pure crystalline Vitamin B-1 has been found to be of great value.

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Vita Nujol is a smooth, pleasant-tasting emulsion of pure mineral oil with pure crystalline Vitamin B-1 added in such quantity that the suggested average dosage is the average adult maintenance dose of that important food factor (400 International Units).

Vita Nujol has a place in the treatment of the majority of constipation cases, and also in the gastro-intestinal syndromes of chronic alcoholism and many other pathological states associated with Vitamin B-1 deficiency.

Vita Nujol has been thoroughly tested and proven in laboratory and clinic.

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It would seem
that all soft curd milk
should be easily digested...
but is it?

The answer to that question has a bearing on the dietary treatment of gastrointestinal disorders.

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*Bulletin 380, The Pennsylvania State College, School of Agriculture and Experiment Station.



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Diffuse Spasm of the Lower Half of the Esophagus*

By

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ESOPHAGEAL occlusion in which an organic lesion is not present at the site of obstruction constitutes a very interesting condition. The better known of such conditions are cardiospasm, localized non-sphincteric spasm and diffuse spasm of the distal half of the esophagus. The last named is the least known of the three conditions and may give rise to a very distressing train of clinical symptoms. For this reason it is indeed essential that we review the anatomic, physiologic and clinical facts concerned with esophageal occlusion. It is the purpose of this paper, therefore, to present such facts, to review typical cases of diffuse spasm, to present a résumé of the clinical and possible etiologic factors responsible and to note the reaction of this condition to various therapeutic agents. For a lucid understanding of the problems concerned in any condition as complex as this, it is well to review first some of the facts as well as some of the controversial points concerning the anatomic and physiologic characteristics of the esophagus.

ANATOMIC CONSIDERATIONS

The esophagus is a muscular tube (1, 2, 3) the proximal portion of which is continuous with the distal portion of the pharynx just posterior to the cricoid cartilage and anterior to the sixth cervical vertebra; it extends caudalward through the posterior mediastinum, through the esophageal hiatus of the diaphragm, and into the abdominal cavity. Its most inferior portion opens into the stomach at a level between that of the tenth and that of the twelfth thoracic vertebra. The mucous membrane is made up of stratified squamous epithelium outside of which there is a thick, tough submucosal layer. The muscularis is composed of an inner circular layer and an outer longitudinal layer, the former predominating in the distal portion and the latter predominating in the proximal fourth. In man, the muscular elements are striated in the proximal third, both striated and smooth in the middle third and smooth in the distal third. Surrounding the muscular coat is a thin fibrous tunica adventitia. The diameter of the esophagus, in general, increases from the proximal portion distalward, the narrowest portion being at the level of the cricopharyngeus muscle. Constrictions are situated also at the level of the aortic arch, the left bronchus and the diaphragm.

The nerve supply is derived from the vagi and the sympathetic chains. Sympathetic fibers are known which come from the inferior cervical ganglia and from the celiac plexus. The existence of direct

branches from the thoracic sympathetic ganglia is still a cause of controversy.

PHYSIOLOGIC CONSIDERATIONS

The function of the esophagus is to convey food and liquid from the oral cavity to the stomach (4, 5, 6, 7). The act of swallowing has been described as occurring in three stages.

Stage 1. After mastication the food is rolled into a bolus and is transported to the pharyngeal entrance by the voluntary action of the tongue and myohyoid muscles.

Stage 2. The mucous membranes of the posterior pharyngeal wall, base of the tongue and soft palate contain sensitive sensory spots, called the chief and accessory spots. These spots are the sites of origin of afferent nerve impulses which are carried over the glossopharyngeal nerve, the second division of the fifth nerve and the superior laryngeal nerves to the center of deglutition in the floor of the fourth ventricle. The impulses thus conveyed institute the second and involuntary act of swallowing. The dependence of deglutition on incoming afferent impulses from special regions in the oral and pharyngeal cavities is illustrated by the fact that deglutition is impossible after thorough cocaineization of the regions in which such impulses originate. Trauma or pathologic processes that affect the center of deglutition make swallowing impossible. This is illustrated in cases of bulbar palsy, amyotrophic lateral sclerosis with bulbar involvement and in certain cases of cerebral thrombosis.

Stage 3. The third stage of swallowing begins when motor impulses are given out from the center of deglutition which set up peristalsis in the esophagus. Three distinct mechanisms exist which control the course of the bolus along the esophagus: (a) The afferent impulse is sent out from the chief and accessory peripheral centers to the center of deglutition in the brain which in turn sends out motor stimuli to different segments of the esophagus to set up peristaltic activity. The continuity of the esophagus is not necessary for this mechanism. (b) The second mechanism consists of a series of reflexes which pass successively through the center of deglutition. Each reflex has its distinct afferent path to the center which in turn sends motor stimuli to definite regions of the esophagus. A bolus of food by its presence locally can precipitate peristalsis. This mechanism is dependent on the integrity of the esophagus as well as on the integrity of the vagus nerves. (c) The third mechanism has been demonstrated by Cannon (8) and Carlson, Boyd and Percy (9). After bilateral cervical vagotomy in the cat the entire esophagus is at first paralyzed. Then the part made up of smooth muscle and Auerbach's nerve plexus is capable of local co-ordination independent of afferent or efferent connections with the central nervous system.

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The vagus nerves and sympathetic nervous system innervate the esophagus. It is generally agreed that the vagus system is the chief course for both afferent impulses from and efferent impulses to the organ. The exact details are not yet clearly understood. The role of the sympathetic nervous system is not definitely known but apparently it does not exercise an antagonistic action toward the vagus nerve so far as deglutition is concerned.

Various changes in the esophagus are capable of producing pain. The (5) mucous membrane is not very sensitive to irritants but painful sensations can be felt as arising secondary to spasm and usually are localized in the lower retrosternal and retroxiphoid regions but may be referred into the cervical and mastoid regions, to the angle of the jaw or into one or both external auditory canals. Pain also may be referred to the back at a level between that of the tenth and that of the twelfth thoracic vertebra.

In the study of esophageal motility, tone and spastic phenomena it is well to keep in mind that experimental work will vary according to the animal used, since the anatomic relationship of esophageal musculature, especially the relationship of smooth to striated muscle, differs in various species. The musculature of the esophagus of the dog and rabbit is striated throughout the entire organ. In cats, apes and man the esophagus is composed of striated muscle in the proximal portion and smooth muscle in the distal portion. The goose has an esophagus composed entirely of smooth muscle. Thus the results obtained in laboratory experiments cannot always be directly applied to human beings.

ETIOLOGIC ASPECTS OF ESOPHAGEAL SPASM

From the standpoint of the etiologic basis of spastic phenomena in the distal half of the esophagus interesting and significant experiments have been performed by Carlson, Boyd and Pearey (9) and Carlson and Litt (10) on cats and on a *Macacus* monkey. Stimulation of the sciatic nerve produced inhibition of tone at the cardia and distal portion of the esophagus in most of the studies. At times, however, contraction followed sciatic stimulation. The effect was present although both vagi were sectioned in the neck. The state of tone in the distal portion of the esophagus was influenced by thermal, mechanical and chemical stimulation of the tongue and mouth. The state of tone present prior to stimulation was important. If the esophagus was atonic, contractions were noticed when the pharynx was stimulated mechanically. If a high degree of tone was present, inhibition was noticed after pharyngeal stimulation. Similar effects were noticed when the central portion of the glossopharyngeal nerve, created by division, was stimulated. These reflexes failed to occur after section of the vagi. Traction on intact vagus nerves, sudden stretching of the stomach, mechanical stimulation of the gall bladder or common bile duct caused severe hypertonus or spasm at the cardia. It was felt that both vagi and splanchnic efferent pathways were involved in these reflexes, since they were obtained in a diminished degree after section of both vagi but were not obtained after section of both vagi and splanchnic nerves.

Strong distention or compression in the urinary bladder, large or small bowel, or cutaneous stimulation produced prolonged contractions or spasm at the cardia. The authors felt that long reflex mechanisms

apparently could be thrown into activity by the stimulation of any sensory nerve in the body.

Veatch (11) stimulated nerve fibers peripheral to the celiac ganglion and the splanchnic nerves in cats and observed more or less maintained tonic contractions on which rhythmic contractions were superimposed in the distal portion of the esophagus in both cases.

The results of the aforementioned experiments are interesting when one speculates as to the etiologic basis of diffuse spasm of the esophagus. Moersch and Camp (12) postulated as to the possibility of reflex origin. Schultz Ortiz (13) and Einhorn and Scholz (14) have called attention to conditions which may precipitate reflex spasms in the esophagus. These spasms may be secondary to lesions within the esophagus itself as in the case of carcinoma, esophagitis or foreign body. They may be secondary to lesions within the stomach such as carcinoma, gastric ulcer or diaphragmatic hernia. They may be secondary to lesions in the gall bladder or biliary tract. Esophageal spasms have been described which have been due to organic disease of the central nervous system, as the result of poisoning with lead, arsenic and belladonna, or in the course of infections or tetany. Sluder (15) observed nonsphincteric spasm of the esophagus in a case in which a positive Wassermann reaction was obtained. The esophageal spasm disappeared after cocainization of the sphenopalatine ganglion. Eloesser (16) has presented four cases of persistent nonsphincteric spasm of the esophagus occurring at the level of osteoarthritic deformities of the spine. Disturbance of innervation secondary to pressure was postulated as being a possible cause.

As can readily be seen, it is extremely important that a primary pathologic process in the esophagus and elsewhere in the body be searched for when any individual has diffuse esophageal spasm.

Comby (17), Jacobson (18, 19), Muggia (20), Brühl (21), Sudhues (22) and Schultz Ortiz (13) have observed cases wherein emotion apparently alone has precipitated rather severe esophageal spasms. It has been our experience to find that in some cases of diffuse spasm of the esophagus emotion plays a definite etiologic part.

CLINICAL SURVEY

A clinical survey of diffuse spasm of the distal portion of the esophagus is interesting but difficult.

Historical. Probably the first description of diffuse spasm of the esophagus was made in 1889 by Osgood (23) who read a paper before the Boston Society for Medical Improvement wherein he told of six cases in which there must have been severe esophageal spasm. All of these patients complained of dysphagia. His description of symptoms was as follows: "The distress was always located beneath the xiphoid cartilage as high as its union with the gladiolus, and here tenderness on pressure is usual. From its point of origin the discomfort, which is very peculiar in character, may radiate up to the pharynx and from that locality pass into one or both ears. . . . When the entire tract of the esophagus is thus involved the distress is very annoying and is apt to alarm the patient. . . . There is the sense of impending suffocation. . . . Sometimes the distress appears to the right of the median line and gradually involves the right chest as far as the outer

border of the mamma, being sharply felt in the nipple. In extreme cases pain is felt in the back. . . . At all times there existed difficulty in swallowing beer, champagne, apollinaris water, and other gaseous drinks. As soon as the fluid reached the lower end of the esophagus a spasmodic, but only momentary, constriction followed. . . . It is during the existence of an obstinate attack that the sufferer complains of a strange sensation of pain in one ear, very rarely both ears, and not at all in some cases. . . ."

Osgood (23) remarked about the unusualness of this syndrome, in that there was "no absolute stenosis" of the esophagus. Unfortunately the diagnosis could not be established accurately due to the fact that roentgen rays had not been known at that time. More recently with accurate roentgenologic examinations of the esophagus diffuse spasm was probably recognized by Teschendorf (24) and by Bárony and Polgár (25), but it remained for Moersch and Camp (12) to describe this condition as a distinct clinical entity.

Diffuse spasm of the esophagus is generally characterized by dysphagia and pain. The dysphagia is intermittent in character at the onset. The point of obstruction is usually situated dorsal to the distal half of the sternum. Variation as to the type of food or liquid which precipitates dysphagia and pain is noticeable. The condition may go on to complete esophageal obstruction which lasts variable lengths of time. This complication may be so severe that a gastrostomy may be necessary. Pain is frequently a very distressing symptom. The pain may simulate that of angina pectoris, or of disease of the stomach or gall bladder. In several instances incorrect diagnoses have been made and thus specific therapy has been directed toward a condition which did not exist. Pain may vary from a dull sense of discomfort to a sharp excruciating pain which may simulate gall stone colic in its severity. Pain is usually situated in the retroxiphoid and retrosternal region but may extend to the back in the neighborhood of the tenth and twelfth dorsal vertebrae or may extend upward along the anterior portion of the thorax into the cervical region and into the external auditory canals and then along the jaw. Pain may be precipitated by meals or it may occur independent of the ingestion of food or liquids since attacks of pain have awakened from a sound sleep individuals who have this difficulty. Almost all patients who have diffuse spasm of the esophagus are of an intense, temperamental makeup. Invariably exacerbations are precipitated by nervous strain, nervous fatigue or anxiety.

Moersch and Camp (12) have described very clearly the roentgenologic changes seen in cases of diffuse spasm of the esophagus. It is desirable that roentgenoscopic observations be performed, because roentgenograms represent only certain phases of the entire picture. Three main types have been listed according to the findings on roentgenoscopic examination: (1) diffuse, irregular spasm in the distal half of the esophagus; (2) multiple spastic segments and (3) diffuse narrowing of the distal half or third of the esophagus. The type may vary in degree and at times during the examination the different types of spasm may occur in the same individual. As barium is swallowed there are rapid changes in the size of the esophageal lumen due to irregular peristalsis. The barium moves up and down with peristalsis. From time to time part of the barium mixture is allowed to

enter the stomach when the distal end of the esophagus dilates slightly. Attention was called to the fact that in the distal end of the esophagus there is a rapid change in the size of the esophageal lumen in contrast to the fixed defect of cardiospasm. Another striking feature of diffuse spasm which helps to distinguish it from cardiospasm is the relatively small degree of dilation that occurs proximal to the involved portion, regardless of the duration of symptoms. In cases of cardiospasm, dilation of the esophagus proximal to the cardia is usually severe.

In some cases the spasm may cause the appearance of multiple regions of regular, concentric narrowing, between which regions portions of the esophagus have the appearance of diverticula. The true nature of the condition is made clear by roentgenoscopic examination.

Esophagoscopy examination of patients who have esophageal spasm may be somewhat difficult because of the nervous instability of many of these patients. There is marked spasticity of the esophagus in the affected portion, the lumen may appear as a dimpled area. Usually, however, by taking an adequate amount of time and without using force, the esophagus will relax and it is possible to introduce the esophagoscope into the stomach. If a cannulated sound is passed over a previously swallowed silk thread spasm in the distal portion of the esophagus can be felt to offer an increased elastic resistance. At times the spasm is so extreme that it is impossible to pass a sound beyond the involved portion. The degree of spasm may vary from day to day, a fact already established by the roentgenologist. At times the passage of a sound is accompanied or followed by pain which is similar to the pain which causes the patient to consult the doctor.

Treatment. An adequate therapeutic regimen for patients who have diffuse spasm of the esophagus is as yet lacking. It is desirable that these individuals avoid fatigue, too much nervous strain and anxiety. Emotional upsets can precipitate exacerbations of the condition. Under an adequate amount of mental and physical relaxation improvement usually occurs.

Esophagoscopy. Diagnostic esophagoscopy gives certain individuals partial relief. At times this procedure has given more relief than dilation by means of sounds that have a larger diameter than the esophagoscope.

Dilation. Dilation is accomplished by the use of sounds and the hydrostatic dilator. These cannulated instruments are passed over a previously swallowed twisted silk thread. Improvement is usually effected but the results are in no respect so striking or satisfactory as the results achieved in cases of cardiospasm.

Drugs. Many drugs have been suggested for the relief of esophageal spasms. Perhaps the most widely used drugs in the past have been atropine and belladonna. Unfortunately, the results have not been uniformly satisfactory. Guns (26) found that atropine caused prolongation of the passage of a bolus through the esophagus. Howarth (27), Guns (26), Doumer and Cuvelier (28) reported good results with the use of papaverine in treating spastic conditions of the esophagus.

The value of having suitable drugs to aid individuals who have diffuse esophageal spasm during an exacerbation is quite evident. For this reason a series



Fig. 1. The effect of morphine sulfate, intravenously, on esophageal contractions; from a case of diffuse spasm of the distal third of the esophagus.

of studies to determine the effect of various drugs on the smooth muscle of the esophagus were conducted by Dr. John McGowan and me (29).

EXPERIMENTAL STUDY

A soft rubber balloon was connected to the distal end of a perforated Sawyer tube. This system of balloon and tube was made airtight and watertight, leaving only the proximal portion of the Sawyer tube open to be connected with a pressure recording device. The pressure recording device was made up of a water manometer with the distal column of water supporting a float with a writing point. A smoked drum was used to record changes of pressure within the system. The balloon and tube were swallowed by the experimental subject and placed in the distal third of the esophagus. Determination of its situation was made by roentgenoscopic examination after the balloon was in place and partially filled with iodized oil. The experiments were conducted with 12 cc. of water in the balloon-tube system. If too much fluid was used esophageal contractions became very active and very difficult to record on the smoked drum. The system was then connected to the recording apparatus. Soon after introduction of the balloon and tube great esophageal activity was observed. This activity was allowed to subside before the studies were started.

RESULTS

Morphine sulfate. Morphine sulfate given intravenously caused prompt and definite relaxation of the smooth muscle in the distal third of the esophagus both in normal individuals and patients who had diffuse spasm of the distal half of the esophagus (Fig. 1).

Amyl nitrite. Amyl nitrite when inhaled caused great temporary relaxation of the distal portion of the esophagus. This effect occurred in normal individuals as well as in patients who had diffuse spasm of the esophagus (Fig. 2).

Benzedrine sulfate. Fifteen milligrams of benzedrine sulfate given through a Sawyer tube to a patient who had diffuse spasm of the esophagus caused a severe drop in intra-esophageal pressure. The esophagus remained quiet for about an hour after which there was a severe increase in esophageal contractions with a severe rise in intra-esophageal pressure which persisted until the experiment was discontinued fifty minutes later because of pain. The patient stated that retrosternal and retroxiphoid pain caused by esophageal spasm could be felt at least two hours after the experiment was discontinued.

Benzedrine sulfate given to normal individuals did not produce any definite effect on the distal portion of the esophagus.

Fifteen units of insulin were given to a normal individual. During the hypodermic injection there was a drop in pressure in the balloon which lasted sixty-four seconds. After fifty-five minutes esophageal contractions became less frequent and finally ceased. During this period the subject experienced definite symptoms of hypoglycemia. During this entire period in which symptoms of hypoglycemia were present there was a rather severe degree of relaxation of the esophagus. Adrenalin, aromatic spirits of ammonia, sodium nitrite, mecholin, metrazol and trethylene

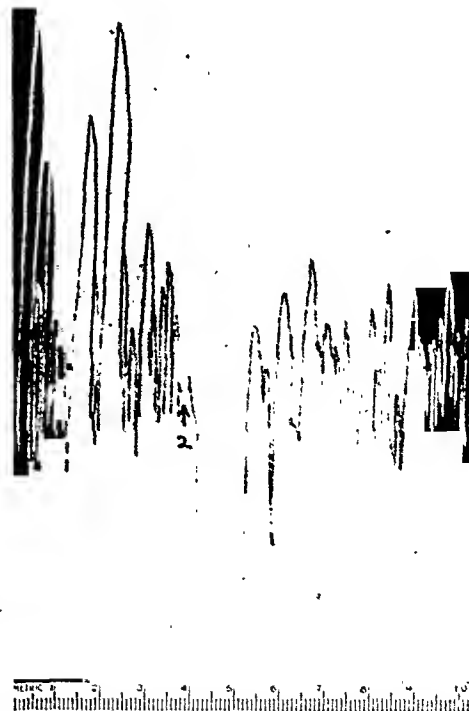


Fig. 2. Relaxation of esophagus of normal person after inhalation of amyl nitrite.



Fig. 3. Severe, diffuse spasm of the esophagus; the gastrostomy tube is shown.

showed no definite tendency to cause relaxation in the distal third of the esophagus.

The results after subcutaneous administration of atropine sulfate were variable. In some of the experiments a severe degree of relaxation was noted but at other times effects could not be observed.

REPORT OF CASES

Between January, 1935, and September, 1938, seventeen patients who had diffuse spasm of the distal half of the esophagus were seen at The Mayo Clinic. Five representative cases will be presented.

Case 1. A white man, sixty years of age, stated that he had had dysphagia for two and a half years before registration at the clinic. He had experienced the "sticking" of food in the lower retrosternal region. His greatest difficulty had been with tap water and salt mackerel. At times he had regurgitated food but at no time had he experienced pain. Two years before coming to the clinic complete esophageal obstruction had developed, and a gastrostomy had been done elsewhere. Since that time he had found it necessary to take almost all food through a gastrostomy tube. Dilatation and esophagoscopy had been performed many times without benefit.

On admission to the clinic, roentgenologic study revealed diffuse spasm of the distal half of the esophagus (Fig. 3). Esophagoscopy revealed that the esophagus was severely spastic. This change was most prominent in the distal third. An organic lesion could not be demonstrated in the esophagus. A detailed history was taken and an examination for some primary condition which might cause reflex spasm was performed. The only significant facts were as follows: (1) In 1920, cholecystectomy had been performed elsewhere, presumably for cholecystitis; (2) the patient had been troubled with bronchial asthma for two years and (3) carious teeth were present.

Novocain was injected in the cervicodorsal region, after which the patient was able to swallow ice water without

difficulty and barium was seen to pass into the stomach. On the basis of the definite improvement which occurred after cervicodorsal sympathetic anesthesia, a bilateral cervicodorsal sympathetic ganglionectomy and trunk resection was performed. After operation the patient was able to eat everything for fifty-two hours and then the esophagus became closed completely. The esophagus was subsequently dilated by means of sounds. Improvement was not noted for a year and a half; then swallowing improved in a remarkable manner until at present he has very little trouble. At times he can eat any food without a bit of trouble. Use of the gastrostomy tube was discontinued more than nine months ago.

Case 2. A white man, fifty-three years of age, had noticed dysphagia for the first time, in 1930, while drinking a beverage that contained caffeine. Soon afterward, dysphagia had developed in relation to solid food and liquids other than this beverage and more recently, a burning sensation had developed in the lower retrosternal region after swallowing solid food. At times, by taking plenty of time and by drinking plenty of water with his meals he had experienced very little trouble. Occasionally, while lying down he had heard "a fizzing sound" coming from the retrosternal region. He had been a heavy smoker, smoking ten to fifteen cigars a day, and had been in the habit of drinking excessive amounts of a beverage containing caffeine each day. He had stopped drinking this beverage and stopped smoking with noticeable improvement in his symptoms. He had been nervous and irritable for the two years previous to registration at the clinic.

Roentgenologic studies showed a severe diffuse spasm of the distal half of the esophagus (Fig. 4). Esophagoscopy was rather difficult to perform because of severe spasm of the distal third of the esophagus. An organic lesion was not visualized. The rest of the examination gave negative results. The patient was given sedatives and was advised



Fig. 4. Multiple spastic segments in the distal half of the esophagus.



Fig. 5. Diffuse spasm of the distal portion of the esophagus.

to avoid too much nervous strain. Recent information regarding his condition is not available.

Case 3. A Jew, aged fifty years, stated that for one year he had had dysphagia. His trouble had begun with solid foods only but soon liquids were found to cause trouble also. At times he could take liquids without any trouble but at other times he would have considerable difficulty with them. He had lost twelve pounds in a year. Roentgenologic studies of the esophagus, performed elsewhere, showed "an ulcer of esophagus."

He came to The Mayo Clinic in May, 1938. The results of physical examination were negative. Roentgenoscopic examination showed spasm at the cardia with diffuse spasm of the distal part of the esophagus (Fig. 5). Other studies, including roentgenologic examination of the stomach and duodenum and routine laboratory tests, gave negative results. A half grain of papaverine was prescribed to be taken three times a day, one-half hour before meals. This was taken for two days and had very little effect on deglutition. The esophagus was then dilated to the size of a No. 41 French sound and 1 grain of stramonium was given twice a day. After four days the patient was able to eat anything without trouble. He was allowed to return home taking 1 grain of stramonium two times a day for two weeks out of four.

Case 4. A white woman, fifty years of age, stated that she had been troubled with belching, flatulence, "sour stomach" and "pressure" in the upper part of the abdomen immediately after eating. Foods such as cabbage, apples, fatty or fried foods and tomatoes had particularly caused trouble. She had noticed definite dysphagia when excited or nervous. At times this had become so severe that she was unable to swallow water. At times she had regurgitated food and liquids.

A tumor about three times the size of a normal uterus was found in the left adnexal region on physical examination. This was believed to be an ovarian cyst. Roent-

genoscopic examination revealed a diffuse spasm of the distal portion of the esophagus (Fig. 6). Roentgenologic examination of the gall bladder, stomach and thorax gave negative results; gastric acid values were: free hydrochloric acid 40, total acidity 52. The basal metabolic rate was minus 12. The routine laboratory tests gave normal results. The esophagus was dilated to the size of a No. 41 French sound after which she was able to swallow better than formerly. An exploratory pelvic operation was advised but was postponed due to the illness of her husband.

Case 5. A white woman, aged seventy years, complained of having experienced rather severe dysphagia since March, 1937. At the onset the dysphagia had been mild but after a period of two weeks, she had experienced severe obstruction of the distal portion of the esophagus. At times she had had rather severe cramps, colicky pains in the superior portion of the epigastrium and in the inferior portion of the retrosternal region. This had been partially relieved by heat. The degree of dysphagia had been variable. At times she had experienced very little trouble and at other times had been able to eat only thin gruels and liquids. She had lost seventy pounds in seventeen months. Her family physician very keenly had observed a spasm in the distal part of the esophagus and had suspected the presence of an intrathoracic tumor.

Physical examination revealed that essential hypertension was present. The blood pressure was 188 mm. of mercury, systolic and 110, diastolic. Roentgenologic studies showed diffuse spasm of the distal half of the esophagus (Fig. 7). Roentgenologic studies of the gall bladder and stomach gave negative results. Routine roentgenologic examination of the thorax revealed calcification and torsion of the aortic arch. The esophagus was dilated to the size of a No. 45 French cannulated sound by passing it over a previously swallowed silk thread. There was considerable spasm felt in the distal part of the esophagus. Stramonium was prescribed but gave no definite relief. Papaverine hydrochloride, 3/4 grain was prescribed to be taken



Fig. 6. Diffuse spasm of the distal portion of the esophagus.

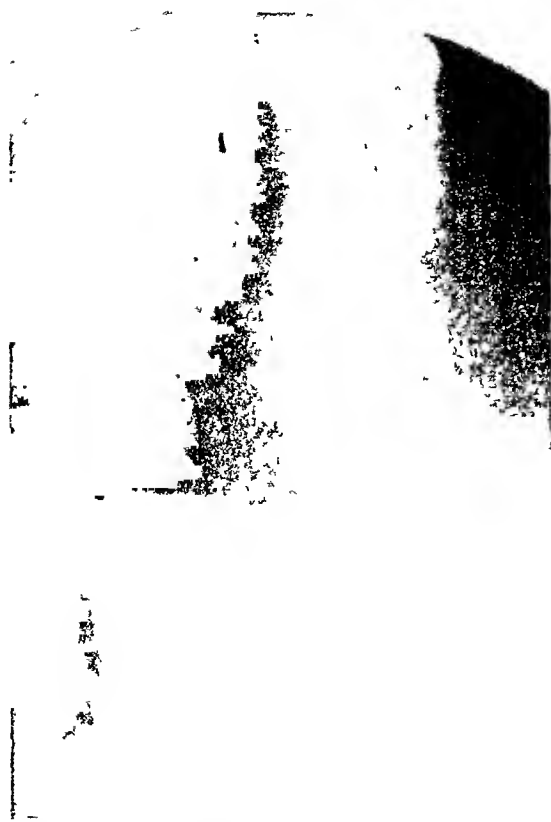


Fig. 7. Diffuse spasm of the distal portion of the esophagus.

a half hour before meals three times a day. The patient stated that this gave a great deal of relief.

COMMENT

In fifteen of the seventeen cases of diffuse spasm of the esophagus encountered at The Mayo Clinic between January, 1935, and September, 1938, this condition was the primary chief complaint. Seven of these patients were women and eight were men. The youngest patient was thirty-one years of age and the oldest, seventy. Other conditions were found in certain cases of the group which might have been partly responsible for the esophageal spasm. These conditions were diverticula of the distal portion of the esophagus, duodenal ulcer, duodenal diverticulum, chronic cholecystitis with cholelithiasis and a pelvic tumor. One patient had asthma, one had diabetes mellitus and one complained of sore gums secondary to dental extraction. Objectively, morphine sulfate and amyl nitrite caused relaxation of the distal part of the esophagus and subjectively, certain patients were helped by the use of stramonium, and others by the use of papaverine.

Two additional patients who showed evidence of diffuse spasm of the distal portion of the esophagus were seen at the clinic during the same period in which the aforementioned cases were observed. Both of these patients came because of serious organic heart disease. One man had had repeated coronary occlusions and had severe hypertension. He stated that cold liquids caused dysphagia and regurgitation.

A second man had severe coronary disease and heart block.

Many highly nervous individuals were seen who complained of transient dysphagia but whose entire examination, including roentgenoscopic examination of the esophagus, gave negative results. These cases were not included in the series.

SUMMARY

It is the purpose of this paper to call attention to a group of cases of esophageal occlusion in the distal portion due to diffuse spasm. A brief review of the facts and controversial points concerning the anatomic and physiologic characteristics of the esophagus is presented. It is of interest to note that spasm of the distal portion of the esophagus can be produced experimentally by the stimulation of various nerves. Spasm has been observed clinically secondary to organic lesions of the esophagus, stomach, gall bladder and biliary tract and in cases of organic heart disease. Spasm of the distal part of the esophagus occurs among certain nervous individuals when they are placed under emotional strain.

Diffuse spasm of the distal half of the esophagus is a condition which is usually characterized by dysphagia and pain. The condition may go on to complete esophageal obstruction. The pain may resemble that caused by disease of the stomach or of the gall bladder or by organic heart disease and for these reasons an incorrect diagnosis may be made and, thus, treatment may be directed toward a condition which does not exist. Pain at times is very severe and is usually situated in the lower retrosternal region but may extend to the epigastrium, to the back, into the neck or ears or to the angle of the jaw.

The roentgenoscopic examination is very important in this condition. Three main pictures have been described: (1) diffuse irregular spasm, (2) multiple spastic segments and (3) diffuse narrowing of the distal half of the esophagus. This is definitely different from that of cardiospasm. Esophagoscopy examination shows evidence of spasm in the distal half of the esophagus.

Satisfactory treatment for this condition has not been evolved as yet. It is important that fatigue, nervous strain, anxiety and emotional upsets be avoided, for they almost invariably precipitate an exacerbation of symptoms. Most of the individuals who suffer from this condition are tense and nervous. Esophagoscopy and dilation of the esophagus by means of sounds and the hydrostatic dilator may give partial relief but the results of dilating the spastic esophagus are in no respect so striking or so satisfactory as they are in cases of cardiospasm.

A method for studying esophageal contractions and the effect of various drugs on the distal portion of the esophagus has been described. Objectively a decrease of tone and of contractions was observed after inhalation of amyl nitrite. The effect was great but transitory. This effect has been observed through the esophagoscope in cases of diffuse spasm of the distal portion of the esophagus. Morphine sulfate intravenously caused rather severe, prolonged relaxation of the distal portion of the esophagus. The administration of atropine sulfate gave conflicting results.

Seventeen cases of diffuse spasm of the lower portion of the esophagus were studied. Possible

primary causative conditions are listed and include traction diverticula of the distal portion of the esophagus, duodenal ulcer, diverticulum of the duodenum, gall bladder disease and organic heart disease. Subjective improvement was observed after esophagoscopy and esophageal dilation as well as after the use of certain drugs such as stramonium and papaverine.

CONCLUSIONS

1. Diffuse spasm of the distal portion of the esophagus is a condition which as yet is not clearly understood.
2. Roentgenoscopic findings associated with this condition are very definite.
3. It is possible for intra-abdominal and intrathoracic pathologic conditions to cause reflex spasm in the distal portion of the esophagus.

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The Problem of Gastric Hyperacidity*

By

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THE term hyperacidity has been used to designate (1) highly acid gastric juice, (2) a very free flow of gastric juice, usually of high acidity, and (3) a group of clinical symptoms, namely, fullness, distress and burning in the epigastrium, at times associated with the regurgitation of "acid" material. It is often stated or implied that the very sour stomach secretion is responsible for the symptoms. We wish briefly to criticize the above concept, but to point out that pathological hyperacidity does in fact occur under special conditions.

Confusion in the subject goes back for many years; indeed, ever since it has been known that the stomach produces acid alleged disorders of secretion have been related to unpleasant symptoms. But most of these

views were based on inadequate or erroneous data. Hilton Fagge, in 1886, representing the best English practice of the time, was apparently unfamiliar with actual measurements of gastric secretion but he refers to "another form of gastric pain" which "begins two to four hours after a meal and lasts for several hours. This writer thought that its seat was in the duodenum. But Sir Thomas Watson points out that one can generally remove it by giving an alkali. . . He therefore supposes that it is due to the continued secretion of gastric juice after the food has passed through the pylorus" (1). By 1894 William Pepper in America was familiar with clinical methods of measuring gastric secretion and, following the German writers, especially Leube, was inclined to relate symptoms to variations of the stomach juices. As regards "nervous dyspepsia" for example he found that "in

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the form which is combined with hyperacidity there is a burning, gnawing pain in the stomach, thirst and sometimes sour eructations, and even vomiting of acid liquid" (2). There was no doubt in his mind that symptoms were due to excessive acidity "for, although the prime factor is, of course, a neurosis, the actual cause of the pain is the local irritation of the terminal filaments of the pneumogastric nerves in the stomach by the acid." It is of interest that despite these views Pepper does not mention alkali as a method of treatment but advises arsenic, nitrate of silver, valerianate of zinc, cocaine, Hoffman's anodyne, hydrocyanic acid and chloroform. "The local application of the galvanic current has proved valuable even in obstinate cases." Coming on to 1914 the situation is not clarified by the information given in Emerson's Text Book on Clinical Diagnosis. The old error of setting up rigid limits of normality is maintained when it is stated that "one hour after the Ewald breakfast the total acidity averages normally 40 to 60 per cent, or 0.15 to 0.22 per cent HCl; over 0.25 per cent means hyperacidity" (3). If one applies this concept literally a person with total acidity of 60 would be normal, one with total acidity of 61 would have hyperacidity, an abnormal state; and the whole subject is clearly reduced to absurdity. By 1930 doubt was being cast on the older views but McCrae in Osler's Practice still felt that there are "some symptoms apparently associated with hyperacidity. . . There is a sense of weight and pressure, with burning in the epigastrium, commonly associated with acid eructations" (4).

The few examples which have been given above to illustrate the confused state of the subject could be multiplied indefinitely; suffice it to say that even at the present time physicians frequently speak of the syndrome of epigastric distress and burning as "hyperacidity" just as they refer to concentrations of gastric acid above certain arbitrary values as hyperacidity. It is evident, then, that certain data are necessary to clarify the question; first the full range of secretion in normal people, both as to acidity and quantity, must be established; and secondly, it must be determined whether the alleged symptoms of "hyperacidity" are directly related to the degree of acid of the gastric juice.

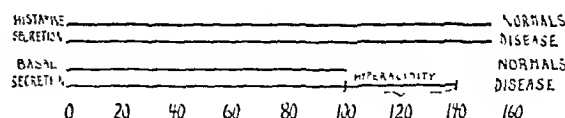
Pollard and Bloomfield in 1931 (5) using a standard histamine test measured the gastric secretion of people who had no evidence of stomach disorder and found that the total acidity varied from 30 to 150. It may be recalled that the latter figure approaches the upper limit of acidity which the stomach is capable of attaining, pure acid gastric juice, according to physiological studies, having a concentration of 0.170 N (6). It is true that the majority of the people in our normal series had a total acidity in the vicinity of 110 to 120, but exceptions were frequent at both ends of the distribution curve. Studying the quantity of gastric secretion in the same group it was found that the highest ten-minute output after histamine stimulation varied from 8 cc. to 70 cc. even though one-half of the determinations fell within the limits of 21 to 35 cc. Pollard in 1933 (7) elaborated the above observations and was able to report on histamine tests in 654 normal people. These studies were adequate for the setting up of definitive standards and fully confirmed the previous smaller series.

Pollard's series of normal people was supplemented by histamine tests on 166 patients with peptic ulcer.

Although it is notable that the most acid and profuse gastric secretion encountered in the clinic is found in patients with peptic ulcer, in no case were the limits established for normals transgressed. It is clear then that inasmuch as the entire possible range of gastric acidity is found in normal people, one may speak of relatively high or low acidity in relation to the frequencies revealed by the distribution curve, but *hyperacidity* is an inaccurate and misleading term, implying as it does disease or at least a state of pathological physiology.

Such are the facts when gastric secretion is explored with the powerful stimulus of histamine. It seemed possible, however, that under other conditions true "hyperacidity" might be demonstrated and this was actually the case when spontaneous or basal gastric secretion was investigated. Basal secretion, briefly, is measured by aspiration of gastric juice in subjects at rest under basal fasting conditions as if prepared for a metabolism test. The total juice is collected over successive ten-minute periods for an hour or more until a steady level of secretion is reached. For further details the paper of Pollard and Bloomfield (8) may be consulted; suffice it to say that such basal secretion reflects the spontaneous influence of autonomic nerves as well as possible intrinsic or humoral secretory stimuli and is to be distinguished from juices produced by histamine or food stimulation. Detailed studies of basal secretion will be published elsewhere, but in the present connection it need only be emphasized that as with histamine juice a wide range of acidity is encountered although the values, on the whole, are of course lower than after histamine. In some 75 people without evidence of organic disease of the stomach the basal total acidity varied from a few degrees up to 97. One patient with Raynaud's disease had a value of 111 and two patients with "indigestion" but no abnormal X-ray findings, had acidities of 110 and 117. As far as our present experience goes one may, therefore, place the upper limit of basal total acidity at approximately 100; it is certainly not over 120. Turning, however, to patients with proven organic disease of the stomach, notably duodenal ulcer, basal total acidity as high as 140 was encountered. Indeed among a consecutive series of 26 cases of duodenal ulcer basal acidity of over 100 was found in 14 and acidity of over 120 in 8. Basal or spontaneous gastric secretion may then exhibit a truly pathological degree of hyperacidity, that is to say a higher acid than is ever met with in normal people under the same conditions of testing. (See Chart 1). The *volume* of basal

CHART 1
RANGE OF ACIDITY IN



gastric secretion showed similar interesting relations. The output per ten-minute period in the normals rarely exceeded 15 cc., whereas among those just mentioned with hyperacidity there were three who secreted 30 cc. or more and eight with ten-minute volumes of over 20 cc. While the highest levels of

acid and volume do not always coincide in the same individual the tendency to a coincidence of hypersecretion and hyperacidity is striking.

The pathological hyperacidity and hypersecretion described above was not necessarily associated with any symptoms and this brings us to a discussion of the second aspect of the problem. Are there any specific symptoms directly due to highly acid gastric secretion? Is the clinical syndrome loosely spoken of as hyperacidity in fact due to a disorder of secretion?

It may be said in advance that a good many physicians simply assume that a "burning" sensation in the epigastrium is due to acid. Acid burns, hence a burning feeling is caused by acid. That this assumption is, however, not necessarily true is shown by very simple experiments. If a small balloon is placed in the esophagus and inflated an unpleasant sensation results. Although all possibility of participation of acid in the genesis of this sensation is eliminated, complaint of a burning feeling is frequently made by the patient. In our series (9) of inflation experiments such statements as "a deep burning," "a prickly pear down there," "finger nail against a hot stove," "sharp burning," or "burning, gnawing pain" were mentioned by the subjects. Similarly, inflation of the stomach produced such complaints as "burning sickish feeling as when he overeats," and with duodenal inflation "a hot sticking pain," "a burning cramp," etc., were mentioned. Furthermore, inflation of stomach or duodenum in patients with indigestion often reproduced their spontaneous discomfort. It is clear, then, that the assumption that burning sensations are due to burning by acid is unwarranted. Further clinical evidence is the occurrence of "burning" indigestion in some people with complete gastric anaecidity. Conversely, as we have pointed out above, it is common to have high levels of gastric acidity without any clinical symptoms at all. The relief of "burning" by soda has been emphasized as proof of symptoms being due to acid, but as we have shown elsewhere (10) such relief

can not be explained by simple neutralization of acid, but it is necessary to assume an alteration of stomach tonus as a result of liberation of gas in the stomach. Finally it must be recalled that indigestion is often relieved by relaxing strain, correcting faulty eating habits and by other measures which produce no alteration of gastric acidity. In brief, all the evidence indicates that symptoms of so-called hyperacidity are due not to acid but to abnormal states of spasm or tension of the stomach or duodenum.

It is of course true that many people with indigestion have high gastric acidity and vice versa. That these two phenomena—hypertonus and hypersecretion—are both the common effects of a certain type of autonomic nervous system rather than one the cause of the other seems to us self-evident, just as glycosuria and acidosis are the common effects of a disorder of metabolism, neither being the cause of the other.

SUMMARY

It may be concluded that the clinical syndrome of so-called "hyperacidity" is spurious in so far as there is no evidence that acid plays a direct part in producing the symptoms. As a clinical designation the term hyperacidity should be abandoned as inaccurate and above all misleading, since the symptoms are generated by motor and not by secretory disturbances.

Certain people, usually with duodenal ulcer, secrete under basal conditions a larger volume of gastric juice of higher acidity than is ever attained in normal asymptomatic individuals. These excessive degrees of acidity may be correctly designated "hyperacidity" but this is a purely physiological (laboratory) diagnosis without definite clinical implications. Hyperacidity is only revealed when spontaneous (basal) gastric secretion is studied, since powerful stimuli such as histamine stimulate as high degrees of acidity in some normal people as are ever encountered in disease.

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The Effect of Pregnancy and of Antuitrin-S on Cinchophen Ulcers in Dogs*

By

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ELSEWHERE (1) we have noted that pregnancy has a beneficial effect on the symptoms of peptic ulcer in women. Experimentally, we have found that daily subcutaneous injections of Antuitrin-S (which

is obtained from the urine of pregnant women) has a beneficial effect on Mann-Williamson ulcers in dogs (2). We tried to determine whether the Mann-Williamson operation when performed on pregnant dogs would produce a lesser percentage of ulcers than when this operation was performed on normal non-pregnant

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animals. However, in our hands, all the pregnant animals aborted soon after this operation, which is, at best, rather a major one.

In searching for another type of experimental ulcer to test the supposed beneficial effect of pregnancy on ulcer, it occurred to us to use the one produced by cinchophen. In man, cinchophen in toxic doses produces liver damage and jaundice. In dogs, there is produced a toxic gastritis followed by multiple erosions, and then a few large penetrating ulcers on the lesser curvature. The animal invariably dies of hemorrhage or perforation unless the giving of the drug is stopped (3-8). Although the ulcer produced by cinchophen resembles human peptic ulcer, it is caused by a toxic gastritis, it is more frequent in the stomach than in the duodenum, and it heals as soon as the use of the drug is stopped.

METHOD

The cinchophen was made into a starch paste (20 gm. cinchophen, 40 gm. starch and 2000 cc. water) and a sufficient quantity of this mixture was given to each dog (mixed with food or via stomach tube once daily) to represent a dose of 100 mgm. per kilo of body weight. Thirty-four healthy dogs were used. Nineteen non-pregnant dogs served as controls and were given the above dose of cinchophen. Nine non-pregnant dogs were given subcutaneous injections of 1 to 5 cc. of Antuitrin-S daily in addition to the standard daily dose of cinchophen. The remaining 6 dogs were pregnant. They were given the above standard daily dose of cinchophen.

RESULTS

I. Ulcer incidence.

1. 19 control non-pregnant dogs fed with cinchophen.

8 died of ulcer, 7 of perforation (longest survival time 88 days, shortest 33 days, average 58 days).

11 were sacrificed after an average period of 85 days (longest 134 days, shortest 47 days). All of these had typical ulcers.

2. Nine non-pregnant dogs fed with cinchophen and injected daily with Antuitrin-S.

Five died of ulcer, two of perforation (longest survival time 90 days, shortest 30 days, average 67 days).

Four were sacrificed (one at 62 days, and 3 at 101 days). All of these dogs had typical ulcers.

3. Six pregnant dogs fed with cinchophen.

Four were sacrificed immediately after parturition. One was sacrificed 80 days after parturition and another died 95 days after parturition. All had typical ulcers.

The ulcers, usually located on the lesser curvature, were the typical large lesions, which have been described by others (3-8).

Microscopically, some of the control ulcers showed considerable fibroblastic proliferation but no epithelialization at the edges. Three of the pregnant dog ulcers and two of the Antuitrin-S dog ulcers showed, in addition to the fibroblastic proliferation, the beginning of epithelialization at the edges of the ulcers. We interpreted this as slight evidences of an attempt at healing.

II. In the experiments of Reid and Ivy (5) all the dogs fed on cinchophen died with gastro-duodenal ulcers within an average of 22.4 days (shortest survival time 7 days, longest 59 days). Our dogs lived 2 to 3 times longer. Ivy used Abbott's cinchophen. We used Merck's cinchophen.

Bringing this to Dr. Ivy's attention, and in an attempt to find the differences in the effectiveness of the two brands of cinchophen, Ivy (9) tested them for phenylquinoline. The older cinchophen supplied by Abbott and used by Reid and Ivy was light brown in color, gave a positive test for phenylquinoline and contained a second unknown impurity. The "newer" cinchophen, a white powder supplied by Abbott, like Merck's cinchophen also a white powder, gave a negative test.

With regards to Merck's cinchophen, Robertson (10) of Merck and Company states: "It is improbable that cinchophen (Merck) contains any uncombined phenylquinoline. The preparation conforms with the N. F. requirements which state that it should not contain less than 99.5% cinchophen and that the melting point shall be between 213 and 216 centigrade. Both of these requirements would insure the absence of any demonstrable quantities of combined phenylquinoline."

Therefore the admixture of a small quantity of phenylquinoline, or the unknown impurity, might be responsible for the increased effectiveness of the Reid and Ivy series compared to ours.

CONCLUSIONS

1. Pregnancy and injections of Antuitrin-S had only slight effect on cinchophen ulcers in dogs.

2. There was a definite difference in the rapidity with which ulcers were produced by two different commercial preparations of cinchophen. This may be due to a small admixture of phenylquinoline or the presence of the unknown impurity in one product and its absence in the other.

3. Mann-Williamson ulcers and cinchophen ulcers respond differently under treatment with Antuitrin-S.

Note: The authors are indebted to Dr. Donald Beaver, pathologist, for the gross and microscopic examinations of the specimens obtained at autopsy. Mr. Harold M. Padolsky assisted in this work.

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The Calcium Content of Gastric Juice*

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INTRODUCTION

RELATIVELY scant attention has been paid to the calcium content of gastric juice although the chemical composition of this fluid has been studied in detail. Rosemann (1) found that canine gastric juice, obtained after sham feeding, contained from 0.07 to 0.22 mg. per cent of calcium. Gamble and McIver (2) reported values ranging from 4.1 to 10.6 mg. per cent in the gastric juice of the cat (Heidenhain pouch secretion). Rudd (3) obtained values in man, varying between 4.1 to 8.6 mg. per cent. Rudd found that the calcium before histamine stimulation, in four cases, was between 3.08 and 6.30 mg. per cent, whereas after histamine, the figures ranged from 2.03 to 6.10 mg. per cent. Calcium was apparently present in smaller amounts in the very acid secretion following histamine, increasing in amount as the acidity fell. Klerks (4) found that the average calcium in the fasting gastric juice of 31 native patients (Java) was 4.4 mg. per cent, in 33 Chinese, 3.4 mg. per cent, and in 32 native students and servants, 3.6 mg. per cent.

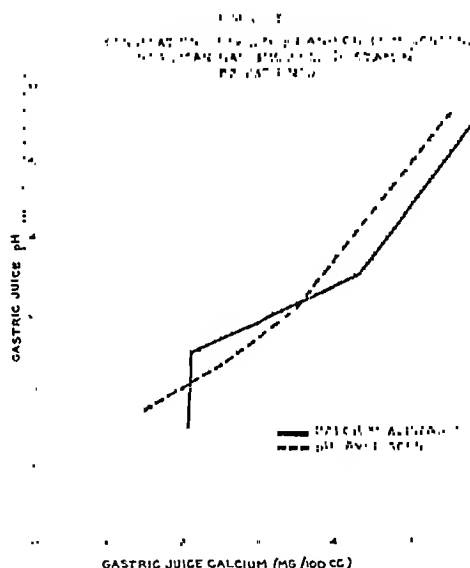
Our interest in this subject was stimulated, during the course of electrolyte balance studies, by the results in five patients in which calcium content of the gastric juice was approximately one-half the serum calcium (Table IV). This finding suggested the possibility that only the diffusible fraction appeared in the gastric contents. To investigate this problem further, the calcium content and hydrogen ion concentration of the gastric juice was determined in a series of 70 patients and five dogs.

METHODS

The gastric juice in five cases was obtained after Ewald test meal, and in sixty-five patients, after the injection of histamine (0.5 mg.). Many of the cases comprising this study were patients with healing or healed duodenal ulcer. Some of these patients were treated with calcium carbonate in amounts up to 35 grams daily. It is notable that the calcium in the gastric juice of these cases was no greater than in patients not receiving calcium carbonate.

The individual samples for each patient were thoroughly mixed and centrifuged at a rate of 1800 R.P.M. Ph determinations were made with the Beckman Ph meter which has a claimed accuracy of 0.05 Ph. The calcium was determined as follows: Two to four cc. quantities of the centrifuged gastric juice were pipetted into special 15 cc. centrifuge tubes, followed by the addition of 2 cc. of water and 1 cc. of saturated ammonium oxalate. The Ph was adjusted to approximately 4.60 using Brom cresol green as the indicator. After standing in the icebox overnight,

the samples were centrifuged and washed several times with dilute ammonia water. Two cc. of 5 per cent H_2SO_4 were then added, and the calcium was titrated with 0.1 N $Kmno_4$, freshly prepared, at 70° C. (5). All determinations were run in duplicate. Triple distilled water was used in preparing the solutions and washing the glassware. The serum calcium and phosphorus were determined in all patients at the time the gastric juice was obtained. The results were



uniformly within normal limits and, therefore, are not recorded on the charts.

RESULTS

The results are tabulated according to the Ph range of the gastric juice. In gastric juice with a Ph range of 1.49 to 1.91 (Table I) the calcium varied from 1.04 to 3.47 mg. per cent (average 2.06 mg. per cent). In gastric juice with a Ph range of 2.00 to 2.94 (Table II), the calcium varied from 0.85 to 3.75 mg. per cent (average 2.12 mg. per cent). In gastric juice with a Ph range of 3.05 to 8.38 (Table III), the calcium varied from 2.40 to 7.00 (average 4.54 mg. per cent). There seems to be a fairly close correlation between the Ph and the calcium content of gastric juice in that the higher calcium and Ph values usually were obtained in the same gastric juice. This correlation is further demonstrated by plotting the average values of calcium and Ph against each other ("lines of regression") as in Fig. 1.

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In five samples of fasting gastric juice, the Ph ranged from 1.61 to 2.19, while the calcium varied from 3.80 to 6.60 mg. per cent (average 4.61 mg. per cent) (Table IV). In five samples of gastric juice obtained after Ewald test meal, the Ph ranged from 1.70 to 4.49, while the calcium varied from 3.30 to 5.30 mg. per cent (average 4.18 mg. per cent) (Table IV).

TABLE I

*Calcium content of human gastric juice (histamine)
pH range between 1 and 2*

36 Patients		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
J. deW	1.49	1.40
G B	1.49	1.01
J P	1.50	1.40
A O	1.50	1.37
G M	1.50	1.75
B C	1.50	1.55
J K	1.50	1.07
J M	1.51	1.55
G H	1.51	2.00
E M	1.51	2.10
K M	1.52	2.11
O B	1.54	1.30
M O	1.55	1.75
L W	1.58	3.47
H S	1.59	1.50
V A	1.59	4.30
W N	1.59	1.70
J S	1.60	2.75
J S	1.60	2.30
J D	1.60	1.20
R W	1.60	1.85
J K	1.61	1.05
D O	1.61	2.10
J M	1.65	1.50
J I	1.68	2.50
R F	1.70	2.20
A O	1.70	2.30
R R	1.71	2.05
M P	1.71	1.55
D W.	1.73	2.57
G A	1.80	1.25
H S	1.84	1.70
J McG	1.89	1.65
F M	1.89	2.97
W K	1.90	1.50
M T	1.91	2.50

TABLE II

*Calcium content of human gastric juice (histamine)
pH range between 2 and 3*

17 Patients		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
B O	2.00	2.90
A Z	2.05	1.85
B K	2.08	1.72
W S	2.10	2.05
M T	2.17	2.45
H I	2.17	2.15
S Z	2.19	3.75
G M	2.21	2.35
W B	2.23	3.30
H B	2.25	2.50
A T	2.29	1.40
J M	2.30	1.70
P B	2.31	1.55
T W	2.35	1.51
D M	2.41	0.85
L Z	2.88	2.00
H G	2.94	3.29

These figures are in close agreement with the results reported by Klerks.

It will be noted that there is more calcium in fasting and Ewald meal gastric juice than in histamine stimulated secretion. Although the patients were instructed to avoid swallowing saliva, the possibility still remains that contamination with saliva accounted for the higher values. To rule out the possibility that calcium was added via the test meal, the following experiment was performed. Eight arrowroot cookies and 400 cc. of tap water (the usual meal) were thoroughly mixed, and two cc. aliquot samples were digested by boiling after the addition of concentrated nitric acid and ammonium persulfate. The samples were then diluted to 100 cc. volumes and analyzed for calcium in

TABLE III

*Calcium content of human gastric juice (histamine)
pH range above 3*

12 Patients		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
F A	3.05	4.00
A N	3.09	4.05
A R	3.36	3.00
H S	3.45	1.75
W G	3.99	4.70
R M	5.02	7.00
M T	5.19	5.65
J M	5.30	3.00
A W	7.02	2.40
E W	7.95	5.25
T B	8.05	5.90
I F	8.38	4.25

TABLE IV

Calcium content of human gastric juice

A Five Patients (fasting specimen)		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
O D	1.61	5.65
P C	1.70	5.30
H C	1.78	6.60
I S	2.00	5.80
D Mc	2.19	4.70
B Five Patients (Ewald test meal)		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
M D	1.70	3.40
T S	1.81	3.30
C G	1.85	3.80
F k	1.91	5.30
F A	4.49	5.10

TABLE V

Calcium content of canine gastric juice

5 Dogs			
Dog	Type of Secretion	pH Gastric Juice	Ca mg./100 cc. Gastric Juice
A (pregnant)	Fasting	2.04	14.50
	Fasting	3.51	13.60
	Fasting	2.10	13.50
	Histamine (0.2 mg.)	2.09	11.07
A (5 days after delivery)	Fasting	2.50	12.50
B	Fundic pouch	1.51	1.40
C	Fundic pouch	1.79	1.10
D	Fundic pouch	1.58	1.10
F	Fundic pouch	1.39	3.30

the manner previously outlined. Calcium was present in the Ewald test meal in negligible quantities.

Except in those patients with achlorhydria, it seems apparent that histamine stimulation yields a gastric juice of low calcium content, an observation made also by Rudd. The exact mechanism of this phenomenon is not yet clear, although it is conceivable that the greater volume of secretion obtained with histamine could, by dilution, account for the difference.

It is of interest to compare the results for human gastric juice with those obtained in the dog (Table V). The calcium in the fasting juice of dog A (pregnant) varied from 13.5 to 14.8 mg. per cent; following histamine stimulation (0.20 mg.), the value dropped to 11.07 mg. per cent, while after delivery, the fasting juice contained 12.8 mg. per cent of calcium. These results were considerably higher than those obtained in man. It should be noted, however, that contamination of the gastric juice with saliva occurred despite all attempts at its prevention. Accordingly, the calcium content of fundic pouch secretion was determined in four dogs. The values, 1.10, 1.10, 1.40 and 3.30 mg. per cent (Table V) approach more closely the results in man. It is impossible to state at this time whether or not the difference between dog A and dogs B, C, D and E, actually represents a significant variation in the gastric juice calcium of pregnant and non-pregnant dogs.

SUMMARY AND CONCLUSIONS

1. The calcium content of gastric juice with a Ph between 1.49 and 1.91 averaged 2.06 mg. per cent (36 patients). The calcium content of gastric juice with a Ph between 2 and 2.94 averaged 2.12 mg. per cent (17 patients). The calcium content of gastric juice with a Ph between 3.05 and 8.38 averaged 4.54 mg. per cent (12 patients).
2. Ewald test meal and fasting gastric juice contains more calcium than histamine stimulated secretion.
3. The gastric juice calcium in one pregnant dog was considerably higher than in man, while the calcium content of fundic pouch juice in four dogs was comparable to that in human gastric juice.
4. The calcium in human gastric juice, in these studies, was fairly well correlated with the Ph; usually the higher the Ph values, the higher was the amount of calcium.
5. The practical significance of these observations requires further study.

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The Effect Upon Gastric Secretion of Introducing Dilute Hydrochloric Acid Into the Duodenum

A Study of Normal Humans and Duodenal Ulcer Patients*

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THE therapeutics of duodenal ulcers has long been concerned with attempts to reduce the acidity of gastric contents. Usually prescribed for the ulcer patient are frequent feedings and alkaline substances which tend to neutralize acid. Another way to achieve the same end would be to lessen, in some manner, the stomach's rate of secretion. As yet no such procedure has become available for practical, clinical application. The experiments herewith reported constitute part of a search for just such a procedure.

The indications are that the stomach of an ulcer patient in the fasting state secretes considerably more gastric juice than is produced in a normal person. Winkelstein (1) has shown that the nocturnal gastric secretion of patients having duodenal ulcer is definitely higher in acid concentration and greater in volume than is that of normal subjects. Consideration of why this is so leads one into the physiology of gastric secretion in general, and, more particularly,

into what the factors are which terminate the usual post-cibal period of active, gastric secretion. Reports by Webster and Day (2), Gray and Ivy (3), Kosaka and Lim (4), Wilhelmj (5), Griffiths (6) and others show evidence of an active suppression of secretion in animals and in man following the post-cibal activity. Some (3) explain this as due to the action of a chalone called "Enterogastrone," formed in the duodenum; others (5) believe that it is the result of factors acting intragastrically. In any event, it appears likely that the HCl of gastric juice plays a role in effecting this suppression. Webster and Day (2), using dogs, showed that introduction of dilute HCl directly into the duodenum causes a significant suppression of gastric secretion. Griffiths (6) claims to have demonstrated a similar effect in humans.

Such observations allow one to postulate as a hypothesis that duodenal ulcers or the lack of healing may be partly the result of a deficiency state. It is possible that patients having duodenal ulcers may lack some important bit of the mechanism causing suppression of gastric secretion; their stomachs, therefore, con-

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tinue to secrete juice so that the total volume exceeds normal amounts. During the day, the excess acid may be masked by the diluting and neutralizing effects of frequent, small feedings. At night, however, feedings are omitted, and the acid gastric juice passes on into the duodenum relatively undiluted. As a test of this theory of deficiency, it is important to attempt to isolate and to define the missing factor. It might thus be possible to supply this factor to the patient having duodenal ulceration, cause his stomach to secrete in a more nearly normal fashion, and thereby eliminate a factor of chronic irritation of the ulcer, i.e., excessive quantities of acid.

We commenced these experiments with two main objectives:

(a) To determine the importance of HCl in the process of suppression of gastric secretion.

(b) To determine whether there is a difference between the gastric secretory curves of duodenal ulcer patients and those of normal subjects, after the introduction of HCl directly into the duodenum.

METHODS

Experiments on Humans Only

Subjects included eight healthy, male medical students, all free from signs and complaints of gastrointestinal disease, and three male patients having symptoms and X-ray evidence of duodenal ulcer in a state of acute or subacute activity.

Preliminary Conditions

Each subject started every experiment in the fasting condition, having had no food for twelve hours or more, and no water for at least two hours.

General Procedure

The subject swallowed a tube into his stomach, which was then emptied of its contents. Usually, immediately thereafter, the "basal secretion" was determined for a period of fifteen minutes. The lower end of the tube was then passed on into the duodenum, its position being checked by fluoroscopy. This was the procedure in each case, regardless of whether or not fluid was to be run into the duodenum, since it established a common mechanical background for each experiment. In every instance, when the lower end of the tube had served its purpose in the duodenum, it was pulled back into the stomach and was left there until the experiment ended.

The Stomach Tube Used

A single tube, Jutte duodenal type, was used in most of the experiments.

It was originally planned to use two tubes, one extending into the duodenum and the other ending in the stomach. Very soon we discovered the impracticability of this, since it permits the stomach to empty too rapidly and facilitates regurgitation of duodenal contents to dilute the gastric contents.

Method of Recovering Gastric Juice

In a few of the earlier trials, the stomach contents were obtained by aspirating periodically with a syringe. Later, constant suction was used, collections

being made at the end of every fifteen minutes. Most of the saliva was excluded by having the subject expectorate as soon as appreciable amounts had collected in his mouth.

Test Meal

The standard test meal used throughout was 300 cc. of a 2% aqueous solution of Liebig's extract, containing 15 mgms. per liter of phenol red (prepared according to Wilhelmj's directions) (8). Use of this preparation seemed justified on the basis of its being a physiological stimulant as well as its being the only test meal to account for the quantitative factors of dilution of the gastric contents.

Analysis of the Gastric Samples

The volume of each sample was recorded, but has not been charted unless it represents the approximate volume of gastric juice. (Some samples containing gastric juice and test meal were not analyzed for volume of gastric juice alone).

The total acidity of each sample was determined, corrections for dilution being made where necessary according to directions by Wilhelmj. Titrations were done with 0.05 NaOH, using phenolphthalein as the indicator. Figures obtained by titration were then translated into terms of clinical units of HCl.

Variations of the Experiment

The one feature common to all of the experiments other than the "normal" or "control" runs was the introduction of HCl in some form into the duodenum. In some instances 0.4% HCl alone was used, in others gastric juice (which contains HCl) was used.

There are four main groups of the experiment.

(1) Normal Subject—0.4% HCl introduced into the duodenum.

(2) Normal Subject—Gastric juice introduced into the duodenum. (Gastric juice obtained from a person other than the subject himself). (Exogenous gastric juice).

(3) Normal Subject—Gastric juice introduced into the duodenum. (Gastric juice previously obtained from the subject himself). (Autogenous gastric juice).

(4) Duodenal Ulcer Patient—0.4% HCl introduced into the duodenum.

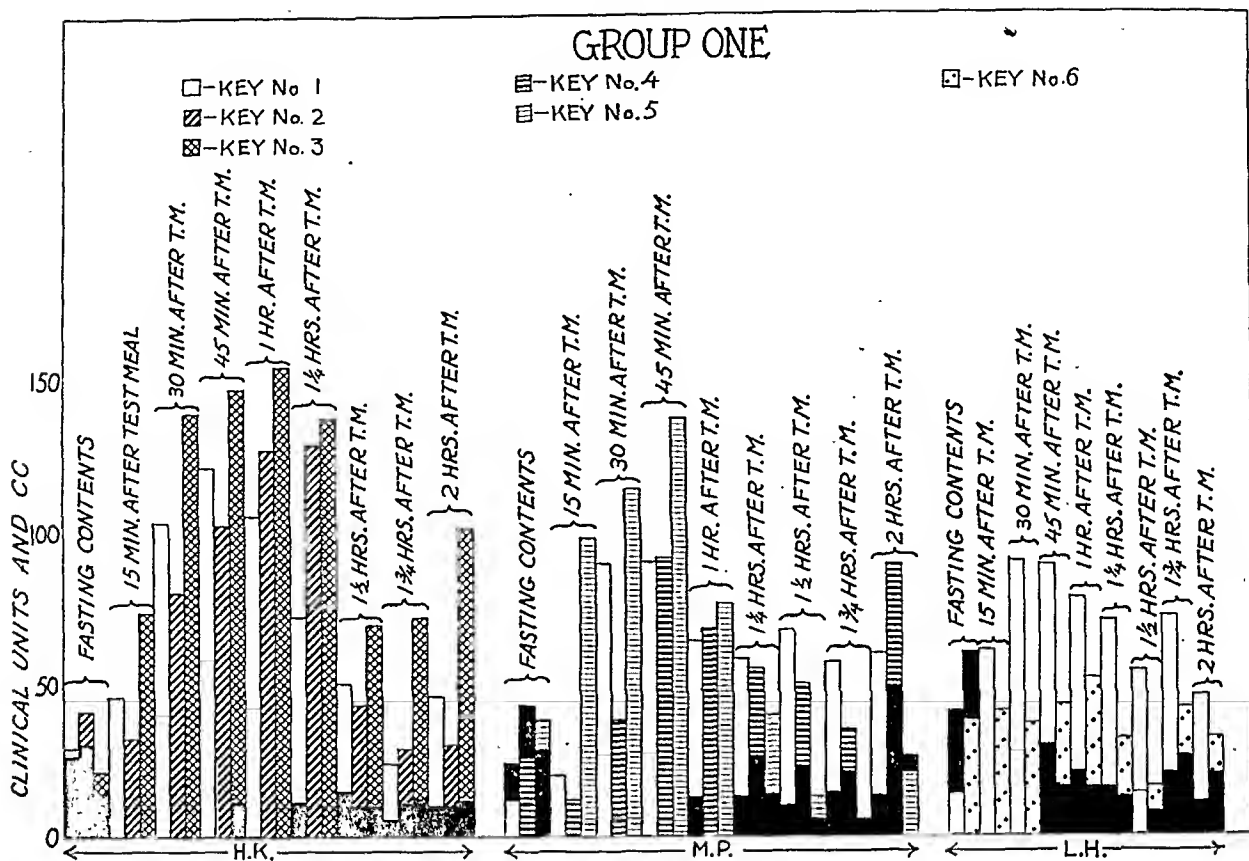
The relation of time of the intraduodenal infusion to giving of the test meal was altered from one experiment to the next. Thus, in one instance, half an hour elapsed between the intraduodenal infusion and giving the test meal. In another, the infusion was allowed to run through the entire length of the experiment. These variations are noted in the charts which follow.

RESULTS

Explanation of Graphs

All solid black columns represent the volume of a specimen expressed in cubic centimeters.

The blank and figured columns represent total acidity expressed in terms of clinical units of HCl. On all of the graphs, Key No. 1 designating the blank columns refers to results obtained when the subject was given the test meal alone; these columns, therefore, represent the "normal" or "control" figures for a basis of comparison.

**Group I**

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

(a) Using test meal alone. (Key No. 1)

(b) Using test meal accompanying and following the introduction of 0.4% HCl into the duodenum. (Keys No. 2, 3, 4, 5 and 6)

H.K.

Key No. 2. These columns represent figures obtained when the test meal was given immediately following completion of $\frac{1}{2}$ hour drip of 0.4% HCl (Vol. 125 cc.) into the duodenum.

Key No. 3. These columns represent figures obtained when the test meal was given $\frac{1}{2}$ hour after completion of an intraduodenal infusion. (120 cc. of 0.4% HCl were dripped into the duodenum over a period of 25 minutes).

M.P.

Key No. 4. These columns represent figures obtained when a drip of 0.4% HCl was continued throughout the period of experiment. (Two tubes were used). Rate of flow was 30 drops per minute.

M.P.

Key No. 5. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (140 cc. of 0.4% HCl were dripped into the duodenum over a period of 30 minutes).

L.H.

Key No. 6. These columns represent the figures obtained when the test meal was given 5 minutes after completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were run into the duodenum over a period of 5 minutes).

Group II

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

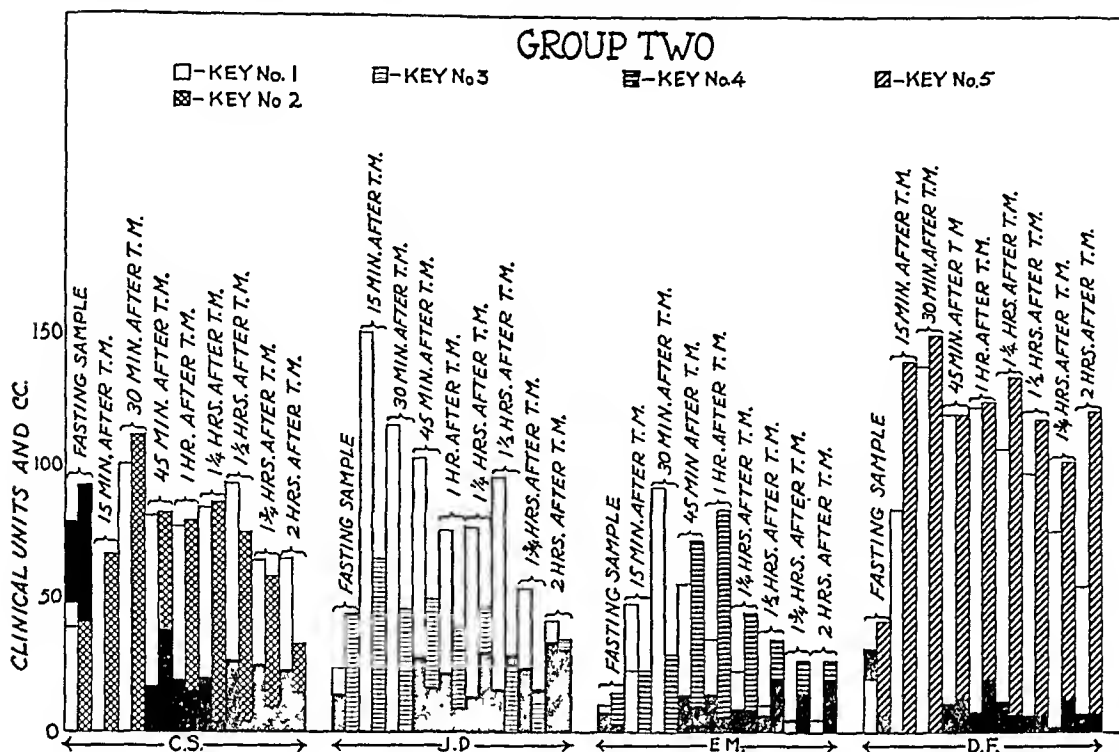
(a) Using the test meal alone. (Key No. 1)

(b) Using the test meal after the introduction of gastric juice into the duodenum. (Gastric juice used for the intraduodenal infusion was exogenous, i.e., was obtained from a person other than the subject). (Keys No. 2, 3, 4 and 5)

Explanation of Graph

In all of the experiments represented by this graph, except for control runs, the test meal was given immediately following completion of an intraduodenal infusion of gastric juice. The keys indicate the source of this gastric juice and the time involved in giving the infusion.

Gastric juice used for the infusion was obtained from a normal subject by using the Liebig extract test meal as a stimulant. Collections were made as usual every 15 minutes. The first four samples were pooled to form the substance of the infusion. Volume and total acidity of the pooled gastric juice were determined in each instance.



The two subjects required for each of these experiments were both present at each trial run; thus there was a minimal delay between obtaining the gastric juice from one subject and infusing it into the duodenum of the other.

C.S.

Key No. 2. 55 cc. of gastric juice obtained from the subject J.D. were infused by gravity over a period of 5 minutes.

J.D.

Key No. 3. 50 cc. of gastric juice obtained from the subject C.S. were infused by gravity over a period of 15 minutes.

E.M.

Key No. 4. 33 cc. of gastric juice obtained from the subject D.F. were infused by gravity over a period of 10 minutes.

D.F.

Key No. 5. 28 cc. of gastric juice obtained from the subject E.M. were infused by gravity over a period of 15 minutes.

Group III

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

- Using the test meal alone. (Key No. 1)
- Using the test meal after the introduction of autogenous gastric juice, i.e., previously obtained from the same subject, into his duodenum. (Keys No. 2, 3 and 4)

These experiments were performed with the idea in mind that some factor or factors other than the HCl

of gastric juice might be responsible for the apparent inhibition of gastric secretion resulting from the interaction of gastric juice and duodenal mucosa; furthermore, that these factors might be specific, i.e., a subject showing no inhibition when gastric juice obtained from another person is introduced into his duodenum might show this inhibition when his own gastric juice is so employed.

A "normal" or "control" experiment was run on the subject. The first four specimens collected after giving the test meal were pooled, and determinations of volume and total acidity were made. This pooled gastric juice was then placed in an ice box for use as the substance of an intraduodenal infusion on the following day. Specimens were not used when more than 24 hours old.

Explanation of Graph

In each of the experiments of this group other than the normal runs the test meal was given immediately following completion of the intraduodenal infusion. The keys thus refer to the experiments and give the volume and time involved in giving the infusion.

C.S.

Key No. 2. 90 cc. of gastric juice were infused by gravity over a period of 10 minutes.

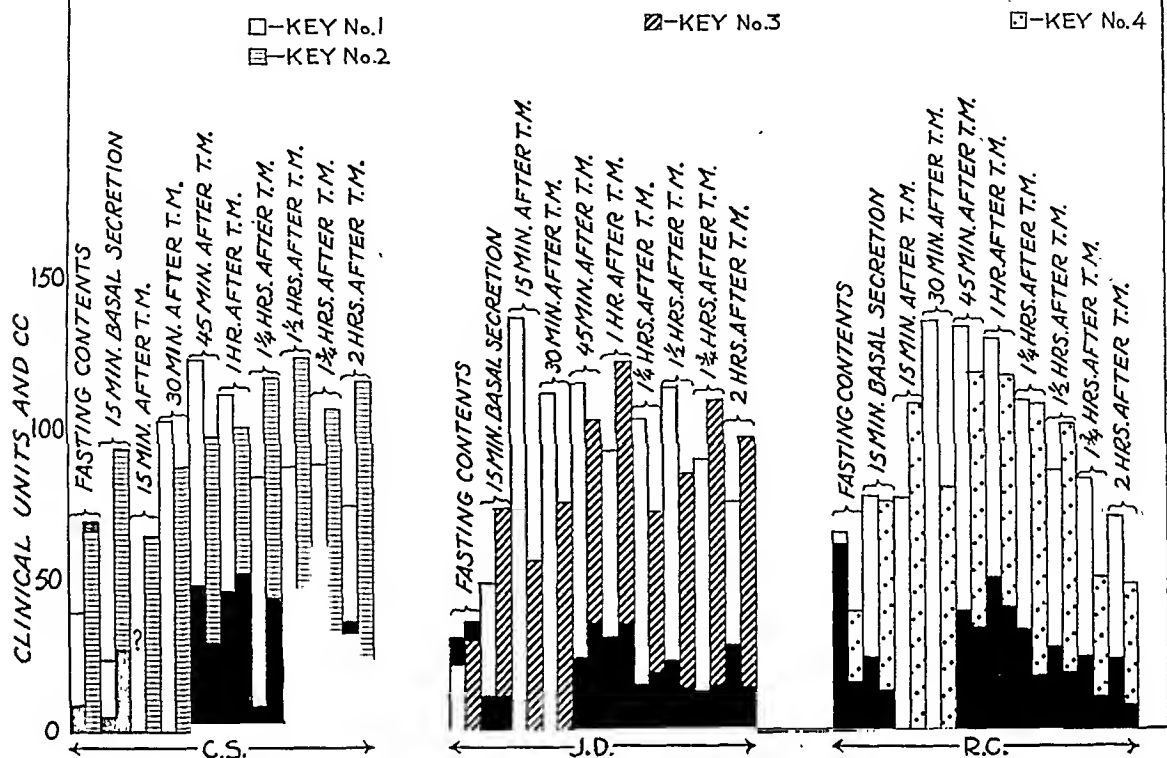
J.D.

Key No. 3. 83 cc. of gastric juice were infused by gravity over a period of 10 minutes.

R.C.

Key No. 4. 139 cc. of gastric juice were infused by gravity over a period of 10 minutes.

GROUP THREE



Group IV

Gastric Secretory Response in Duodenal Ulcer Patients to Liebig Extract Test Meal:

- (a) Using the test meal alone. (Key No. 1)
 (b) Using the test meal after the introduction of 0.4% HCl into the duodenum. (Keys No. 2, 3 and 4)

Explanation of Graph

J.M.

Key No. 2. These columns represent figures obtained when 0.4% HCl was allowed to drip into the duodenum throughout the entire experiment. (Two tubes were used. The rate of flow was about 30 drops per minute).

S.F.

Key No. 3. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were dripped into the duodenum over a 15 minute interval).

E.C.

Key No. 4. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were run into the duodenum over an interval of 3 minutes).

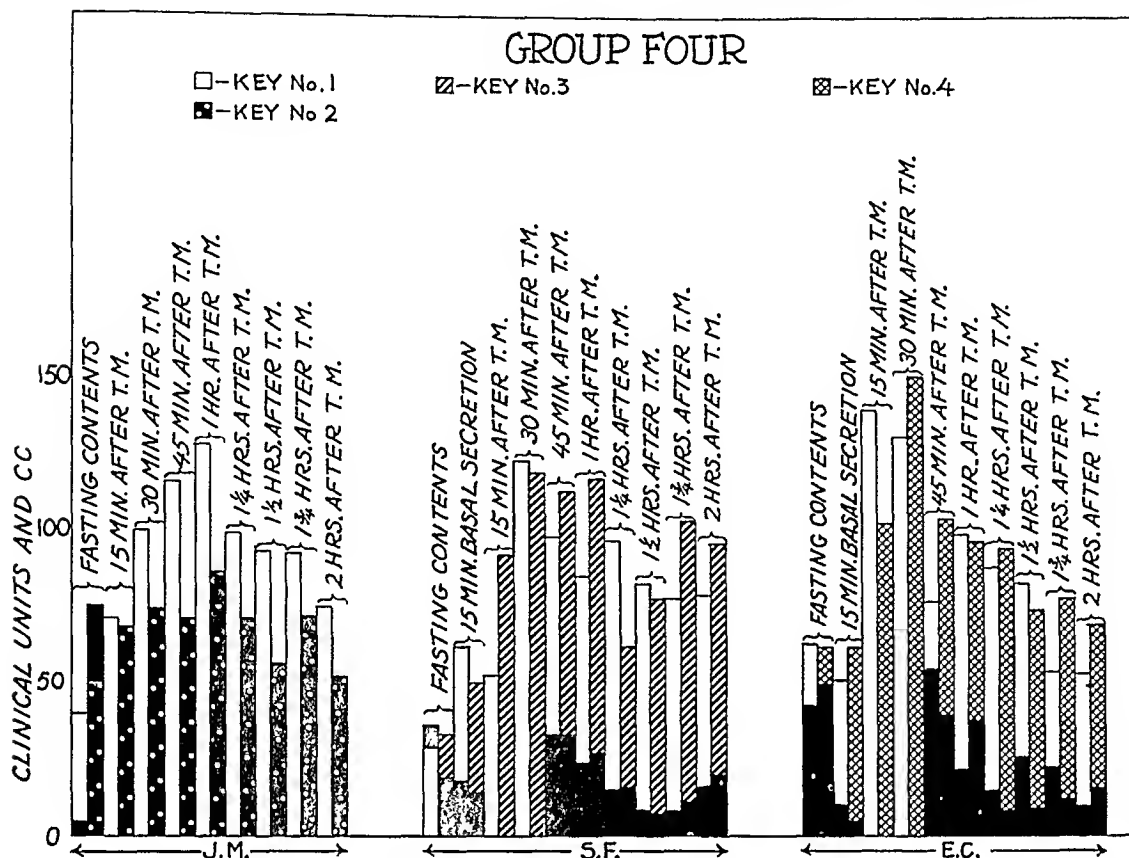
DISCUSSION

Considering our results as a whole, there is no consistent trend indicating any momentous suppression of gastric secretion under the conditions of our experi-

ments; individual instances seem to indicate at least a temporary suppression, but repetition of the same or of a related experiment on the same subject failed to confirm such a suppression. Furthermore, there are no indications that the gastric secretory response of duodenal ulcer patients is significantly different from that of normal subjects, following an intraduodenal infusion of 0.4% HCl.

This does not necessarily disprove the work of the experimenters mentioned in the introduction, since the conditions of the experiments were different. Webster and Day worked with dogs, and the suppression which they obtained by introducing HCl directly into the duodenum was during the intestinal phase of gastric secretion. Griffiths worked with humans; but he used an alcohol test meal, and a mixture of NaCl, HCl and glucose for the intraduodenal infusion. We attempted to maintain the conditions of our experiments on as nearly a physiological basis as possible. For this reason, we used a meat extract test meal and set the concentration of HCl at 0.4%. When it had become apparent that an intraduodenal infusion of 0.4% HCl would not suppress gastric secretion, we replaced the HCl with normal human gastric juice thinking that other factors plus the HCl might effect gastric suppression. However, this is apparently not so.

It is possible, of course, that the strength of the stimulus is so great that it masks the evidence of a suppression which actually does exist. Thus it may be that we were mistaken in trying to cope with the



gastric phase of secretion. The next logical step is to see whether HCl in the duodenum will suppress or abolish the intestinal phase of gastric secretion. Implications in the literature are not very definite concerning details of the intestinal phase of gastric secretion in humans. Possibly it is a prolonged intestinal phase in duodenal ulcer patients which is responsible for the secretion of relatively large quantities of gastric juice. Any practical means of stopping the intestinal phase of secretion would therefore be a valuable addition to our therapeutic armamentarium.

It appears likely that if suppression of gastric acidity is to be attained, it will be done by reducing the volume of acid secreted and not by reducing the concentration of the acid as it is secreted by the parietal cells.

CONCLUSIONS

HCl in 0.4% solution or in gastric juice, when introduced into the duodenum of normal subjects, had no

constant, significant effect on gastric secretory curve.

HCl in 0.4% solution, when introduced into the duodenum of duodenal ulcer patients, had no constant, significant effect on gastric secretory curve.

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Lymphogranuloma Venereum Surgical Aspects

By

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THE very serious surgical problems presented by lymphogranuloma venereum have not received adequate consideration up to the present. The likely reason is that this condition is classifiable among the venereal diseases and thus escapes a thorough evaluation from the surgical point of view. The object of this report is to present the various means of surgical therapy employed thus far; their advantages and shortcomings.

In its various clinical manifestations, lymphogranuloma venereum presents essentially inflammatory lesions of the different organs affected. The disease picture is very similar to other inflammatory lesions appearing in acute, sub-acute or chronic stages. From the point of view of surgical therapy, the laws governing surgical intervention apply, for the most part, in this disease as they do in other inflammatory diseases. An important point of difference between lymphogranuloma and bacterial pyogenic lesions is the fact that this disease is the result of an infection by a filtrable virus. Bacteriologic cultures of pus removed from diseased tissue are sterile. It differs also in the fact that although the anatomic structures involved are those in the pelvis primarily the disease process itself is nevertheless systemic (1, 2). The extent of the inflammatory lesion will depend upon the amount of destruction that will take place because of the activity of the virus, both locally and systemically. With this in mind, a direct approach toward local therapy alone, would appear inadequate to combat this disease effectively. On the other hand, a combined systemic and local therapy seems more rational.

The natural course of the disease process in its primary lesions, inguinal, rectal and genital manifestations, as compared with cases treated, will serve to evaluate the surgical procedures alone as they have been employed thus far.

THE PRIMARY LESION

The acute primary lesions on the genitalia or elsewhere in the body, such as occur in accidental inoculation or by perversion, require no surgical therapy. They are generally evanescent in character and regress spontaneously within a period of two weeks.

THE LOCAL ADENOPATHIES

Inguinal or femoral glandular enlargement will begin from one to three weeks after the onset of the initial lesion. The progress of the lesion is rapid and reaches its height in about three weeks. By that time, that is, six weeks after contact, the glands begin to subside or promptly go on to suppuration. Spontaneous subsidence occurs in about 30% of the cases in a large series (3). The remainder, if untreated, will ultimately break through the skin and form one or more

spontaneous sinuses, which will drain for a variable length of time.

The choice of surgical procedures in these conditions consists of:

1. Incision and drainage.
2. Excision of all diseased tissue, with or without drainage.

3. Bilateral block dissection of the inguinal nodes.

Where incision and drainage were employed, the time of disability was approximately two weeks in the hospital, and from one to seven months for dressings, before a patient was discharged (4).

Block dissection of the lymph nodes yielded better results from the point of view of time. Healing took place within a period of two months.

Since the iliac and other pelvic lymph nodes are simultaneously involved in about one-third of the cases observed, the probability of the removal of all of the diseased tissue is very remote. The fact that elephantiasis of the genitalia may take place after a complete extirpation of the inguinal nodes, also militates against the use of this procedure. It is interesting to note that no drainage was used in two cases and that healing by primary union took place in spite of the presence of frank pus. Complete closure was used, in view of the fact that the pus present was sterile to the usual culture.

The pelvic lymphadenopathy does not create any surgical problems. No case of suppuration breaking through the peritoneum has thus far been reported. An iliac abscess which yielded 300 cc. of pus was observed by the author. The abscess broke through the skin spontaneously above Poupart's ligament and then subsided. Pelvic exudates have been observed but none drained. Abdominal pain due to a mesenteric adenitis necessitating laparotomy, has been reported (2). Without any treatment or with radical surgical therapy, most of the cases seen healed completely at the end of seven months.

With the introduction of a combined systemic and local treatment, the results have proved more satisfactory. In 176 cases only 40% came to suppuration and among the latter, aspiration of the local pus collection in addition to the use of intravenous Frei material sufficed for healing in an average period of six weeks. Among these cases there was no necessity to perform any operative procedure besides aspiration. Sinus formation at the point of puncture took place in few instances. Repeated aspiration was necessary in a minority of cases. Where a sinus formed, the administration of the Frei antigen hastened a spontaneous closure without resort to any other surgical means. In a number of cases where fluctuation was already present, the intravenous therapy was sufficient to cause a complete absorption of the local suppuration, and regression of the entire disease process. The systemic therapy in the inguinal variety of this disease is very

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encouraging and points toward conservative rather than radical procedures as adjuvants in attempts at cure (4). Surgical treatment of the inguinal bubo was contraindicated by John Hunter, as long ago as 1786 (5). He advised his patients to avoid the surgeon as much as possible during the affliction and take a rest cure instead. For the most part his advice still holds true.

RECTAL LESIONS

The natural course of the rectal lesions is one that leads to chronicity. The lesions present range in order of severity from:

1. Fistulas in Ano.
2. Perianal-Condylomas.
3. Acute and chronic proctitis due to pederasty or secondary to previous inguinal and pelvic adenitis.
4. Ulcerative procto-sigmoiditis.
5. Rectovaginal fistulas.
6. Rectal stricture, which may be tubular or diaphragmatic in type.

Although the rectal lesions have been seen to develop as early as six weeks after exposure (6), the usual duration of the rectal lesion is at least two years before it is seen. Thus the examiner is most often faced with a chronic inflammatory lesion.

The procedures suggested for radical cure up to the present, have been as follows:

1. Complete resection—Lahey method.
2. Abdominoperineal resection with preservation of the sphincter ani.
3. Perineal approach with sacral anus.
4. Mobilization of the rectum with excision of perirectal scar tissue.
5. Permanent colostomy with subsequent dilatation of the stricture.
6. Temporary colostomy.
7. Dilatation, with or without anesthesia.
8. Incision or excision of fistulous tracts.

The follow-up of a large series of cases by Anschuetz, Peterson (7) and Frei (8), has proved the operative mortality in the complete operation, in many stages or in one stage so disastrous, that the further use of the procedure is to be discouraged.

The causes of failure are evident when the procedure is attempted. The mobilization of the diseased rectum is extremely difficult. The normal anatomic planes of cleavage are entirely obliterated and replaced by inflammatory scar tissue in which active inflammatory elements may be demonstrated as long as twelve years after the onset of the disease (4). The mesosigmoid likewise become shortened by contiguity to the inflammatory lesion below. This most often prevents an adequate mobilization for a successful anastomosis. Preservation of the sphincter is a practical impossibility in most cases, because the perianal tissue is most often itself involved. Over 75% of the rectal lesions reported are tubular in type. In the remaining group the lesions are diaphragmatic in nature. In any event, the portion of the rectum distal to the lesion is most often involved and cannot be used in the repair.

Another most important cause of failure and high mortality is the fact that as long as there remains any evidence of activity of the disease, one must assume that a phlegmonous type of inflammation is still present in the endopelvic fascia. Attempts at dissection in such tissue is analogous to incision of a phlegmon elsewhere and carries with it the risk of a

lymphatic spread of the disease. Among all authors such radical procedures are cautioned against.

Radice classified (9) his rectal lesions as freely movable or fixed in the pelvis. He suggested that the tubular stricture of the fixed type be treated by colostomy, while the diaphragmatic freely movable, by dilatation. This procedure is reasonable. One report reveals 31 colostomies performed among 160 cases, and in only one case was it possible to close the colostomy subsequently (10). The question of using colostomy as a permanent or temporary procedure necessarily will depend upon the indications present.

Dilatation alone is contraindicated in the presence of active proctitis or periproctitis and is associated with severe general reactions. Because of the severity of the systemic symptoms, this procedure has been abandoned at the Presbyterian Hospital (1). Dilatation may be used with impunity and good effect in cases of chronic stricture, where the active disease has subsided and where the stricture actually represents the healed stage of this disease. In such cases proctoscopy will reveal a smooth mucous membrane, sometimes atrophic and in many cases showing stratified squamous epithelium which grew upward from the anal margin to replace the columnar epithelium which sloughed in the process of repair. Mathewson (11) is particularly impressed with the efficacy of dilatation alone.

Colostomy however has to be resorted to as an emergency procedure at times. Gutman (1) mentions three cases of deaths from peritonitis due to perforation after obstruction due to lymphogranuloma of the rectum. Although such cases are fortunately rare, they must be kept in mind when they do arise.

Temporary colostomy with isolation of the distal segment for rest and irrigation may serve to prepare the patient for an eventual healing of his disease.

The operation of "Evacuation of the Perirectal Space and Retroproctitic Mobilization of the Stricture" reported by Gomez (12), has failed to yield the results claimed for it. It has thus far resulted only in stirring up any latent infection in the endopelvic fascia and has always produced recurrences which were worse than the original condition for which the operative procedure was undertaken. In cases of healed strictures of the "ring" type, this procedure becomes unnecessary, since dilatation alone is sufficient. In tubular stricture where latent inflammatory foci are always present, the procedure is both dangerous and entirely unsatisfactory, since no mobilization is possible. All of the pelvic structures are agglutinated into a compact mass.

The suggestion of Lockhart-Mummery (13) may well be followed as a general principle in the treatment of inflammatory rectal strictures.

"To ascertain the type and extent of the stricture, it is advisable to examine even with partial dilatation, so that the upper limits can be explored and the condition of the proximal bowel immediately above verified. Sigmoidoscopy may thus be performed under anesthesia if necessary. This should be done with great care and splitting of the rectal wall when inflammation is present, should be avoided. In suitable cases the stricture is dilated and treated by continual cleansing. Results of internal proctotomy with subse-

quent dilatation are excellent and permanent, if the patient will endure the inconvenience of dilating long enough to counteract the contraction of scar tissue."

In case of partial obstruction, colostomy may be optional. However, colostomy may be delayed or possibly entirely avoided by the use of the intestinal tube for abdominal decompression, described by Abbott and Johnston (14). After the distension is relieved, sufficient time may be taken for a thorough investigation of the case in point, and the most suitable course followed.

Colostomy as a general rule should be seriously considered in cases of fulminating lesions which do not react favorably to palliative measures or attempts at immunization with Frei antigen. Cleansing of the distal loop and rest, have proved very useful and permitted a late closure in some cases. This is illustrated in the case reported here.

Treatment with Frei antigen intravenously alone, i.e., 0.3 cc. of antigen every other day, has proved disappointing in these rectal lesions from the point of view of complete resolution. The treatment which takes many months to show appreciable changes, is, nevertheless, definitely of benefit to the patient. A noticeable symptomatic improvement is promptly obtained. The bloody purulent discharge becomes less and any painful defecation markedly improved. The constitutional symptoms are promptly relieved. The patients gain weight and lose their sense of weakness. Their general sense of well being is restored. After months of treatment the local lesions show a tendency to healing. The progressive nature of the disease is altered to a state of a chronic, slowly healing lesion. The late lesions generally observed are those which have gone on to spontaneous healing and consequent stricture formation of those in the process of fibrosis.

Incision and drainage or excision of fistulas leave chronic sinuses and lead eventually to recurrences. Radical surgical procedures among this group are exceedingly unsatisfactory.

Palliative methods such as rest in bed, low residue, high vitamin diet, retention enemata of olive oil or cottonseed oil and rectal irrigations with tannic acid solutions, or quinine bisulphate 1:4000, have been used with benefit to the patient.

From the foregoing one may reasonably conclude that radical surgical procedures alone or palliative methods alone are inadequate for either palliation or cure. A rational combination of both palliative procedures and the more conservative surgical methods seem the most advisable course to take at present.

The earliest treatment of rectal stricture by four incisions of circular bands with a bistoury and subsequent dilatation, is recorded by Dupuytren in 1854. Colostomy was successfully performed in 1710 by Littre' (15). Thus the treatment advocated at present is relatively old and simpler in comparison with the more radical procedure envisaged by Von Volkmann in 1887. However, reliance on less radical means seems more advisable until the systemic disease itself is controlled. Then, and then only will the mortality due to the radical removal be reduced. And it is possible to conjecture that the radical procedure may then become unnecessary.

GENITAL LESIONS

The genital lesions observed may be enumerated as follows:

1. Periurethral ulcerations and edema obstructing the urinary flow with resulting urinary retention.
2. Penile lesions—bubonuli and paraphimosis.
3. Elephantastic lesions of the vulva with overhanging pendulous masses.

The surgical problems presented by the chronic genital lesions are first those related to the establishing of a correct diagnosis by biopsy. This is a necessary procedure to exclude other known pathologic lesions such as tuberculosis, syphilis, and carcinoma. The pathologic lesion on the genitalia although not pathognomonic, is nevertheless suggestive of the disease in question and is thus most important. The main problem of surgical therapy is associated with the relief of stenosing lesions of the genital orifices—i.e.: the urethra, and vagina. Among these lesions it was not found necessary to resort to cystotomy in any case reported thus far. The more conservative methods sufficed to cause the more acute edematous lesions to subside. Among this group as in the rectal group of lesions it is important not to attempt repair of any fibrotic distorted parts until the disease process has completely subsided. Excision of pendulous condylomas may then be done and satisfactory healing may be expected.

In view of the above discussion, the treatment of two cases of rectal lymphogranuloma observed at the Gouverneur Hospital is presented.

CASE REPORTS

Case 1—History: P. C., a 56 year old white male, was admitted to the surgical service of Dr. Frank J. McGowan on November 6, 1937.

The patient had vomited repeatedly for thirty-six hours and suffered moderate abdominal distention. Three hours before admission he became extremely weak, perspired profusely and suffered a general collapse.

Eighteen years before the present admission, i.e.: in 1919, a cecostomy was performed because of a "severe inflammation of the rectum." After local treatment of the rectal lesion, the cecostomy was finally closed ten years later, i.e.: 1929. Between 1929 and 1937 the patient had suffered repeated attacks of subacute intestinal obstruction. The attacks were ascribed to incarceration of a right inguinal hernia which was, however, always reducible.

Examination: The patient appeared acutely ill and in shock. The abdomen was moderately distended. The inguinal canals were both clear. No masses were felt in the abdomen.

On rectal examination a definite stenosis was encountered at 5 cms. from the anal margin. The rectal wall was, however, fully movable in the endopelvic fascia. The stricture was annular and barely admitted the tip of the index finger. Proctoscopy confirmed the digital finding. The mucosa was pale and shiny. In the region of the stricture the mucous membrane had a cobble stone appearance, bled easily. Islands of squamous epithelium were seen running along the rectal wall with scarring suggestive of healing of a previously acute lesion.

Laboratory findings: The Wassermann reaction was three plus. The Frei test was markedly positive. A biopsy specimen from the region of the stricture revealed rectal tissue showing chronic inflammation. There was no evidence of any specific lesion.

Course: In view of the signs and symptoms of subacute intestinal obstruction, a temporary sigmoidostomy was

performed by Dr. Francis M. Conway. When the abdominal cavity was explored, the constriction could be felt in the rectum below. The entire colon above the line of stenosis appeared free and uninvolved. The colostomy functioned well and the distal loop was cleansed with saline. Three weeks after colostomy the patient was taken to the operating room and the stricture dilated, with bougies. Very little trauma was caused by this procedure. The mucous membrane above the stricture was found, by sigmoidoscopy, to be entirely clear and uninvolved.

The patient was observed for two months, during which time the colostomy was permitted to close. Rectal dilatation with a large bougie was performed every other day. There was no evidence of recurrence of the stricture. The patient was asymptomatic when discharged, three months after admission to the hospital.

Case 2—History: E. G., a 40 year old colored woman, was admitted to the surgical service of Dr. R. Franklin Carter on March 20, 1936.

She complained of difficulty in passing her bowel movements, for two years. Her symptoms became worse six months before admission. She had passed blood streaked fecal material on different occasions. She had had no previous operations. She had a number of still births but no live children. The patient was known to have had syphilis for three years, for which she had received two intravenous injections of arsphenamine.

Examination: The patient was well developed and well nourished. Her pupils were unequal and irregular. Both ankle jerks and knee jerks were sluggish. The abdomen was soft, no masses were felt.

Rectal examination revealed a narrowing at 3 cms. from the anal margin, which did not admit the tip of the index finger. Proctoscopy revealed a stricture of the rectum at 3 cms. The mucosa was pale and smooth. There was no evidence of any acute lesion.

Course: A cecostomy was performed. Three weeks later the stricture was dilated under spinal anesthesia. This procedure revealed a diaphragmatic stricture which was dilated with little trauma. The patient made an uneventful recovery and was discharged one month after admission.

Laboratory findings: The Frei test was positive. The Wassermann test was negative. The spinal fluid Wassermann was negative.

A biopsy of the rectal tissue showed chronic non-specific inflammation.

Readmission: July 25, 1936. The patient returned to the hospital because of a persistent sinus at the site of the cecostomy. During this three months interval, she had normal, regular bowel movement and no complaints except the presence of a purulent discharge from her abdominal sinus.

The cecostomy sinus was closed. When the patient was examined, the rectum was found to be narrowed, beginning at the internal sphincter. The rectum felt thick and indu-

rated. The constricting band was again thoroughly dilated. She was discharged 16 days after admission.

Readmission: September 10, 1936. The patient was readmitted because of an attack of La Grippe.

Rectal examination showed a well dilated rectum. There was no evidence of stricture.

She had one bowel movement daily without difficulty. The cecostomy wound was completely healed.

DISCUSSION

Two cases of rectal lymphogranuloma are presented. One in a white male and the other a colored female. In both cases the lesions seen upon examination represented diaphragmatic narrowing of the rectum as healed stage of a preexisting acute proctitis. Both of these cases were amenable to conservative surgical therapy.

CONCLUSIONS

1. Lymphogranuloma venereum is a systemic disease, in spite of the fact that its external manifestations are mainly lesions in the pelvic region.
2. The disease lymphogranuloma venereum in all of its manifestations presents essentially lesions which are due to the results of inflammation in any of its stages.
3. These lesions range from the acute exudative processes to the final chronic proliferative or fibrotic conditions of the various structures affected.
4. Surgical treatment alone, or palliative therapy alone have thus far proved inadequate for the complete cure of this disease.
5. Surgical indications in lymphogranuloma are identical with those in any other inflammatory conditions.
6. Surgical intervention is found most useful and least harmful when both systemic and local symptoms and signs have subsided.
7. The most useful procedures in all of the lesions seen in lymphogranuloma are the conservative ones, in combination with local palliative, and systemic Frei antigen intravenously.
8. Thus, for the inguinal adenopathy, aspiration and Frei antigen are suggested.
9. For the rectal lesions temporary or permanent colostomy as indicated; dilatation where possible in combination with local palliative and systemic Frei antigen intravenously are advised.
10. For the chronic genital lesions, conservative surgical therapy after complete subsidence of the inflammatory lesions is deemed most satisfactory.

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Intravenous Modification of the Hippuric Acid Test for Liver Function*

By

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THE hippuric acid test for liver function, which the author introduced in 1933 (1), has technical advantages as well as disadvantages. Its simplicity requires no comments; its inexpensiveness makes it widely available; and the fact that it requires no intravenous injections is a significant advantage when veins need to be conserved, or are difficult to inject. The chief disadvantage is the occasional vomiting which may occur after the oral administration of sodium benzoate. At times too, it is burdensome to collect four hourly specimens of urine. To meet these difficulties the author with Ottenstein and Weltchek (2) presented an intravenous modification.

Recently Lipschutz (3), unaware that such a test had been presented, also published an intravenous method which is very similar in some respects to our modification. Thus, Lipschutz injects 2 gm. of sodium benzoate dissolved in 20 cc. of water, while we give 1.77 gm. in the same amount of water. This little difference is obviously of no importance. His test, however, differs distinctly in one particular, and this leads to an erroneous interpretation. He collects the urine for two hours, determines the amount of hippuric acid excreted during this period, and from this calculates the per cent of the injected benzoic acid which is excreted. Lipschutz thus introduces a concept which is at variance with the original idea of the test. In my test the per cent of administered benzoic acid which is excreted as hippuric acid does not enter into consideration. As a matter of fact, approximately 75 per cent of the benzoic acid given to a normal adult is excreted and 25 per cent is lost, presumably burned in the body. There is no evidence that the amount of benzoic acid which fails to be excreted is related to hepatic dysfunction. The fundamental idea on which my test is based is the measurement of the rate with which hippuric acid is synthesized. In my comprehensive study of the conjugation of benzoic acid in man (4), I established the fact that irrespective of the dose of sodium benzoate administered, the maximum amount of hippuric acid formed per hour is practically constant. This is illustrated in Chart 1. The most rational explanation is that the amount of glycine which the liver can synthesize and conjugate with benzoic acid is limited, and that the hippuric acid output therefore measures the maximum functional capacity of the liver. If hepatic damage occurs, the hourly output is definitely diminished as has been repeatedly confirmed clinically. It is therefore essential that in both the oral and in the intravenous test an amount of benzoic acid be given in excess of the liver's capacity to conjugate within a fixed period of time. This can be readily illustrated by the data of Table I. When a normal subject is given 1.77 gm. of sodium benzoate intravenously, he will excrete 0.7 to 0.95 gm.

of benzoic acid as hippuric acid during the first hour and only from 0.13 to 0.36 gm. during the second hour. Obviously only the first hour measures the maximum functional capacity of the liver to synthesize hippuric acid. From these results, 0.7 gm. benzoic acid has been accepted as the minimal normal hourly excretion. A patient who excretes 0.5 gm. of benzoic acid during the first hour after receiving sodium benzoate intravenously would be reported as having a functional efficiency of 70 per cent. Such a patient, however, will in 2 hours excrete approximately 1 gm. of benzoic acid, and on the basis of Lipschutz's interpretation would be considered normal because he is excreting as much

TABLE I

The excretion of hippuric acid following the intravenous injection of sodium benzoate

Subject	Weight	Hippuric acid (expressed as benzoic acid) excreted	
		1st Hour	2nd Hour
	Kg.	Gm.	Gm.
1	62	0.71	0.31
		0.73	0.36
2	70	0.95	0.16
		0.91	
3	73	0.84	0.13
		0.92	
4	84	0.76	0.30
5	65	0.82	
6	73	0.79	
7	75	0.82	
8	78	0.54	0.31
9	70	0.90	0.28

1.77 gm. of sodium benzoate (equivalent to 1.5 gm. benzoic acid) dissolved in 20 cc. of distilled water was injected intravenously.

benzoic acid in 2 hours as subject No. 1 of Table I, who, nevertheless, has a normal functional liver.

The procedure for the intravenous hippuric acid test as it is employed in my laboratory and in various hospitals and clinics is as follows: The test is done preferably in the morning after the patient has had a light breakfast. A solution containing 1.77 gm. of sodium benzoate (equivalent to 1.5 gm. of benzoic acid) in 20 cc. of distilled water is given intravenously. At least 5 minutes should be taken for the injection. The patient is instructed to void before the test, and to collect the urine exactly one hour after the completion of the injection.

The urine is carefully measured and solid ammonium sulfate added in the proportion of 5 gm. for every 10 cc. of urine. When the salt is dissolved the urine is

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either filtered or centrifuged. Enough concentrated hydrochloric acid is added to make the urine distinctly acid to Congo red or to thymol blue. Usually 1 cc. of the acid is sufficient, but it is absolutely necessary to check with an indicator paper. An excess of acid is permissible. The solution is vigorously stirred until the precipitation of hippuric acid is complete. After

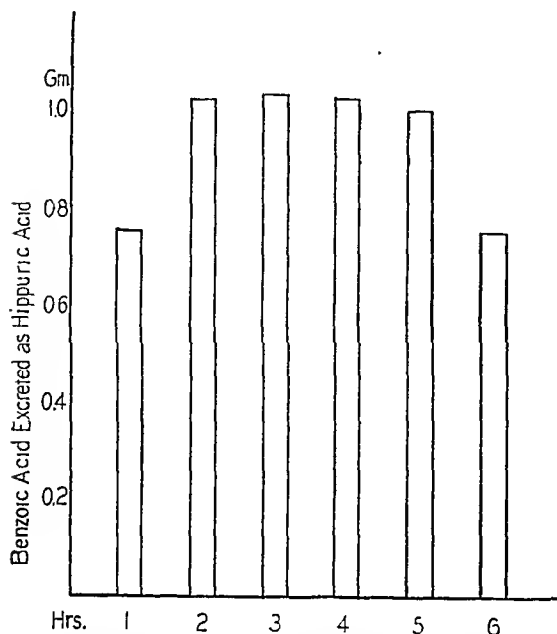


Chart 1. The constancy of the rate with which hippuric acid is synthesized. The subject, an adult male weighing 77.5 kg., was given 9.4 gm. of sodium benzoate by mouth, and the output of hippuric acid for the ensuing 6 hours determined.

30 minutes the crystalline product is filtered, washed with a small amount of cold water, and dried. By using a 4.5 cm. filter paper on a 2.5 cm. filter plate, the hippuric acid can be weighed without removing it from the filter paper. Another filter paper of the same size can be used as counterweight.

To the weight of the hippuric acid, must be added the quantity remaining in solution. Approximately 0.1

gm. of hippuric acid will remain dissolved in 100 cc. of urine containing 50 gm. of ammonium sulfate. To convert the weight of hippuric acid to benzoic acid, one multiplies by 0.68. A normal adult will excrete 1.0 gm. or more of hippuric acid (equivalent to 0.68 gm. of benzoic acid) in 1 hour after receiving sodium benzoate intravenously. For convenience 1 gm. of hippuric acid can be taken as the standard for normal. This will obviate the necessity of converting the hippuric acid to benzoic acid for calculation as has been the custom in the oral test.

The intravenous modification of the hippuric acid test is not intended to replace the original oral test, but is offered as an alternate method. In the new test certain precautions must be observed. It is essential that the sodium benzoate solution be properly prepared to make it safe for intravenous use.* Furthermore the patient must be able to empty his bladder completely at the end of the test. Often it is advisable to have the patient drink a glass of water before the test to increase the volume of urine.

The accuracy of the determination of hippuric acid has been distinctly increased by adding ammonium sulfate before precipitating the acid. Weichselbaum and Probst (5) found that the solubility of hippuric acid is decreased by adding sodium chloride to the urine. Their contribution prompted the investigation of other salts, and it was found that ammonium sulfate is even better than sodium chloride.

*Ampules of sodium benzoate for the test have been prepared by Hynson, Westcott and Dunning, Baltimore, and by George A. Breon and Co., Kansas City.

SUMMARY

A technique for carrying out the intravenous modification of the hippuric acid test for liver function is described. The excretion of 1 gm. of hippuric acid in one hour after 1.77 gm. of sodium benzoate has been injected is recommended as the standard for normal.

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The Use of Pectin-Agar Mixtures in Diarrhea

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SIMPLE summer diarrhea is one of the many vexing problems which confront not only the pediatrician but the general practitioner. The literature pertinent to the subject is quite extensive yet no specific explanation or therapy is even now apparent. It is commonly stated that in infancy "hot weather, in-

fections and artificial feeding" (1) are the causative factors, but it is not the purpose of this paper to discuss etiology or to criticize methods of therapy. Certain general remarks, however, may be in order. The two most commonly employed therapeutic procedures are (1) high protein diet, or (2) starvation, with slow return to normal food intake. The use of

high protein is based on the theory that diarrhea is caused by excessive fermentation of carbohydrate with the production of lower volatile fatty acids which act as intestinal irritants. The harmful nature of such volatile fatty acids is much in doubt. Holt and McIntosh (1) say: "Restriction of the carbohydrate intake may diminish the production of these acids without curing diarrhea, and, conversely, a high carbohydrate diet does not, as a rule, produce any noticeable aggravation of the condition."

The starvation regimen, ordinarily successful, is not ideal because excessive loss of weight frequently ensues, the too prompt reintroduction of the usual formula occasionally leads to exacerbations, and the support of the mother is difficult to elicit because her whole nature demands that she feed her hungry child. It has been stated that there is an inability to digest food during diarrhea, but apparently the only evidence in support of this common belief is that food passes more rapidly through the gastro-intestinal tract. It is also of interest that this same thought was used as an argument when it was customary to starve typhoid.

Winters and Tompkins (2) in this country first suggested the use of pectin and agar in the treatment of diarrhea. Their therapy was not new, but their whole method and procedure was novel. For some years apples had been claimed valuable in treatment of diarrhea. The reasons underlying the success following their use are vague. Moro claimed the effectiveness of apples was due to tannic acid (3). Heisler would also give credit to malic acid and to the mechanical cleansing of the intestines (4), while Scheer places most emphasis on indigestible bulk (5). This latter author successfully fed "agar milk" for diarrhea (6). Malyoth (7) believes pectin and cellulose are the active agents.

Various colloidal substances (pectin, hemicellulose, agar, gums, etc.) are claimed to be effective in the treatment of diarrhea. The physical or chemical properties of such materials are used to "explain" their successful use. Principal emphasis has been placed on their ability to enmesh and cause the evacuation of bacteria (8) and toxins (9), but also their hydrophilic properties are believed to be important (10).

In examining the literature on pectin, it is interesting to note the many reasons why it is believed to be of physiologic value to the body; e.g.:

1. It is bactericidal* (13).
2. It is a source of galacturonic acid—a detoxifying mechanism (14).
3. It absorbs toxins and even poisons from the intestinal canal (9).
4. It is hydrophilic (10).
5. Its buffering action makes milk more readily digestible and should favor the growth of certain organisms (15).
6. It is soothing and healing to the inflamed and ulcerated gastro-intestinal tract (10).
7. It reduces blood coagulation time (16).
8. It helps relieve constipation (17).

Data to prove any one of these hypotheses are likewise scanty, but when all were added together it awakened our interest in the therapy of diarrhea as originally proposed by the Indianapolis investigators.

*A second publication by the Indianapolis investigators (11) attributes the sole bactericidal quality to pH rather than to any peculiar characteristic of pectin. Prickett and Miller (12) concur in this finding.

Experimental: At first we hesitated to accept the large amount of carbohydrate suggested by Winters and Tompkins. Possibly our thought in this was conditioned by the hypothesis that carbohydrate fermentation is especially culpable in diarrhea. We therefore planned to compare the effect of pectin and agar mixtures with and without added carbohydrate. Through the courtesy of the manufacturers,* we obtained a preparation similar to that employed by Winters and Tompkins, with the following composition:

<i>Preparation A</i>	
Pectin	6.3%
Agar	4.3%
Dextri-Maltose No. 1	89.4%

The other preparation employed had an identical ratio of pectin to agar, but no added Dextri-Maltose. Its composition was:

<i>Preparation B</i>	
Pectin	59.4%
Agar	40.6%

The two preparations were added to milk in quantities sufficient to supply equal amounts of pectin and agar.

All cases seen were in private practice. The majority were treated at home and hospitalization was employed only in the severe cases requiring parenteral fluids or transfusions or when the patient lived too far away. A total of 32 cases was followed on Preparation A and 16 cases on Preparation B.

Making the Formula: The preparations were made as recommended: the necessary amount of the experimental preparations (16 level tablespoonfuls of Preparation A or 2½ level tablespoonfuls of Preparation B) was placed in double boiler with a pint or 24 oz. of whole milk and cooked for 15 minutes, poured into 8 custard cups, and allowed to cool. One or more cupfuls was used at each feeding. The gel strength is greater with the smaller amount of milk, and this was used with the older children (i.e., those that had been weaned); for infants on the bottle the more dilute preparation was preferred. By enlarging the hole in the nipple the dilute formula is readily administered. For the older children, chocolate or various fruit flavors were added as desired by the mother. Because Preparation B was not particularly palatable, saccharine, gr. ½ to the pint, was ordered.

The pectin-agar and pectin-agar-Dextri-Maltose diets were started without a preliminary starvation. Water was forced, but no other food or medication was given except parenteral fluids when severe dehydration was present. No feeding by gavage was necessary. Many children requested more of the diet than was prescribed, and the mothers were instructed to supply ad libitum. Preparation A was much more popular with the children and with the mothers than Preparation B.

In prescribing each diet the mother was told that she might meet with resistance when first giving the mixture but that by adequate zeal and

*The preparations employed were supplied by Mend Johnson and Company of Evansville, Indiana. Our Preparation A is referred to by them as Laboratory Product No. 83; our Preparation B, as Laboratory Product No. 102.

urging on her part the child would probably be over the diarrhea in a day or two. The only children who initially refused the preparation were "spoiled"; the majority took it with no protest, but even with a degree of enthusiasm. The greater number of mothers in this group were well educated and only a few of the less intelligent had to be given additional moral support to continue the formula. By outlining clearly the feeding plan at the first visit one can be relieved of much annoyance in the nature of future telephone calls.

Stools were regularly forwarded from the office of the clinician (K.) to the bacteriological laboratory. For physical reasons it was not possible to obtain a

TABLE I
Classification of cases

Diagnosis On First Examination	Clinical		Bacteriological Classification	No. Cases	
	Group A	Group B		Group A	Group B
Diarrhea	18	12	<i>Escherichia</i> and others	11	8
Dysentery	14	4	<i>Salmonella</i>	4	3
			<i>Shigella</i>	4	—
			Not cultured	10	5

stool for culture from each child, but the survey accomplished gave us a fairly complete idea of the type prevalence of organisms in our community during the summer of 1938.

Results: The degree incidence of different bacterial flora in the stools is given in Table I. With the exception of the fact that no dysentery organisms were found in the stools of infants in Group B, the predominating organisms were principally of the *Escherichia* and *Salmonella* groups. Perhaps the sole value of the bacteriological studies was to show that dysentery organisms were not particularly prevalent during the study. As a fact of some interest, the clinical diagnosis on examination has been similarly recorded. As such estimates are based solely on physical findings, the figures in Table I suggest that the infants in Group A were sicker than those in Group B.

In Table II the various objective data are summarized in so far as is practical in a study of this kind. Unfortunately, and entirely by chance, the youngest infants, and those whose illness had persisted for the longest average time with the larger average number of stools were placed on Preparation A. This would confirm the similar conclusions from Table I. In spite of this the infants receiving the carbohydrate-containing preparation (A) responded better than those receiving merely the pectin-agar mixture. The only objective measure of effectiveness was the number of days after institution of therapy before normal stools appeared. Using this measure, Group B appeared slightly superior, but because diarrhea had persisted in Group A for a much longer period of time, and the infants in this group were younger, we are inclined to

discount any semblance of superiority for the B-preparation.

Three deaths were observed during this study. One child was comatose on admission to the hospital with a severe dysentery and incontinent bowels. The second child had been unsuccessfully treated for six weeks by three physicians who had finally referred the case. The diarrhea had shown great improvement just before death, which was from bronchopneumonia and inanition. The third death was due to sepsis from dermatitis gangrenosa infantum after recovery from the diarrhea.

Fever, except in the one case complicated by pyelitis, disappeared within 24 to 36 hours; dehydration, when severe, was treated with parenteral fluids, but if mild, was satisfactorily relieved by the diet alone. Excoriated buttocks healed within 36 hours in most instances. When gross blood was reported in the stools at the onset, it disappeared on the average by the 2nd day of therapy.

Several observations relative to the two preparations are pertinent:

1. In general the children took Preparation A better than B, even though saccharine was added to the latter.

2. There seemed to be less vomiting by those infants who received Preparation A, as compared with infants receiving B.

3. Mild acidosis disappeared more promptly with Preparation A than with Preparation B.

4. There was no evidence of increased fermentation (flatulence) through the use of Preparation A in spite of its high carbohydrate content.

In all cases distention disappeared on administering either of the two pectin-agar materials. As indicated in Table II, either preparation is satisfactory for the treatment of diarrhea promptly and effectively.

DISCUSSION

Normal stools are to be expected within approximately 3 days after Preparation A is incorporated in

TABLE II
Summary of cases

	Preparation A	Preparation B
Number of Cases	32	16
Av. age in months	18.7	33.3
Av. days of illness prior to treatment	6.2	1.4
Av. number of stools per day prior to treatment	9.3	6.9
Av. temperature when first seen	100.7	101.1
Av. day on which first normal stool appeared	3.2	2.4

the diet. With mild diarrhea the character of the stool will return to normal within 12 to 48 hours. This new therapy appears to be superior to other procedures because of the prompt return of the child to normal, together with the fact that there is no concomitant weight loss, and, the gradual return to full caloric intake decreases the possibility of complications.

After normal stools have returned, it is important that the transition to the regular diet be slow. When the stools appeared small, not watery, and moderately

frequent (not over 3 to 4 daily), bananas, jello, cottage cheese, or dry toast were offered at some one feeding. The following day thin soups, cereals, or skimmed milk were tried. In young infants on milk formulae the regular feedings were gradually restored via skimmed milk feedings. Children vary so much in their ability to take food that one must learn how to return a child to a full diet chiefly by experience. Naturally a return of the diarrhea calls for a prompt return to the pectin-agar diet for a day or two.

It is admittedly difficult to make a statistical comparison of diarrhea treated in different ways. Clinical impressions are sometimes more valuable in a disease of this nature than mere average figures. The senior author has had considerable experience in summer diarrhea as seen in private practice, and it is believed that this treatment offers the best approach to successful therapy. It is, of course, not a panacea for all disturbances nor is it a substitute for intelligent pediatric care, but it comes nearer to being the one satisfactory approach than any other thing yet tried.

In spite of early fears that the extra amount of carbohydrate was to be avoided, the study was concluded with the feeling that this is an added desirable feature. We adhered to the original suggestion of Winters and Tompkins and much against our early thought used whole fluid milk in all formulae. This seems to have a definite advantage. There was no evidence of inability

to use or digest the food, and in practically all the cases there was evidence of a prompt return to normal gastro-intestinal function.

Especially interesting was the rapid disappearance of toxicity. The remarkable improvement in the appearance of these children was the most outstanding feature of the study. To see a child in a moribund condition respond in 24 hours and appear almost well is a phenomenal thing even with the miracles of modern medicine. The prompt return of normal stools is most gratifying because there is not then the continual loss of body fluids through diarrhea that leads to acidosis, dehydration, and eventual complications.

CONCLUSIONS

Thirty-two cases of diarrhea seen in private practice were successfully treated with high caloric feedings consisting of whole milk, pectin, agar, and Dextrin-Maltose. Comparison was made with a second group of 16 infants receiving identical formulae save for the added carbohydrate. All cases responded satisfactorily, but the addition of carbohydrate is believed to be a desirable procedure.

On the basis of past experience in the treatment of diarrhea, we believe the addition of pectin, agar, and Dextrin-Maltose to a whole milk formula is a safe, effective, and satisfactory treatment.

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Perforation of a Gall Stone Into the Stomach With Resulting Pyloric Obstruction: Case Report With Gastroscopic and Surgical Findings

By

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FOREIGN bodies in the stomach are amazing for their variety. They have been discovered by clinical, roentgenological, surgical and post-mortem examinations and are usually divided into three groups: (1) swallowed objects, (2) bezoars formed within the

stomach, and (3) foreign bodies which have entered the stomach through or within the abdominal wall.

Under the last classification cases have been reported (1) of the development of a fistula between the gall bladder or a biliary duct and the stomach by the passage of a gall stone.

In this article we are reporting a case with symp-

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toms of pyloric obstruction produced by a gall stone which had passed directly from the gall bladder into the stomach.

CASE REPORT

A 62 year old married man entered the Strong Memorial Hospital on September 26, 1938. He began to have acute

crampy abdominal pains, three months previously, following the drinking of a glass of beer. Pains continued to appear intermittently from a few minutes to two hours after eating. Three weeks ago he developed flatulence and nausea. He vomited undigested food particles without blood. In the past two weeks he had vomited practically all the solid foods ingested. Medication gave no relief. His appetite fell off and he had lost 6-7 lbs.

The only past history of consequence was an attack of biliousness described as "yellow vomiting" about one year ago. In the interim he had occasional flatulence and heart burn.

The physical examination was essentially negative except for congenital clubbed feet and a large degree of brown pigment in the skin of his left leg.

Laboratory examination: Wassermann was 3+ in the cholesterol antigen, negative in the other antigens. Kahn was 3+. Stools were negative for occult blood. A gastro-intestinal roentgenographic examination on September 29, 1938, revealed on the first swallow of barium a round translucent area in the pre-pyloric region of the stomach. Peristalsis came up to this area but no waves passed by. The rugal pattern was interrupted by this defect. The



Fig. 1. Roentgenograms interpreted as benign tumor causing pyloric obstruction.

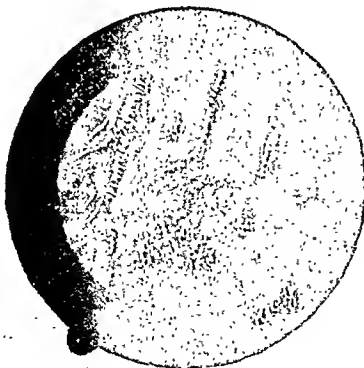


Fig. 2. Gall stone in the stomach as seen by gastroscopy.

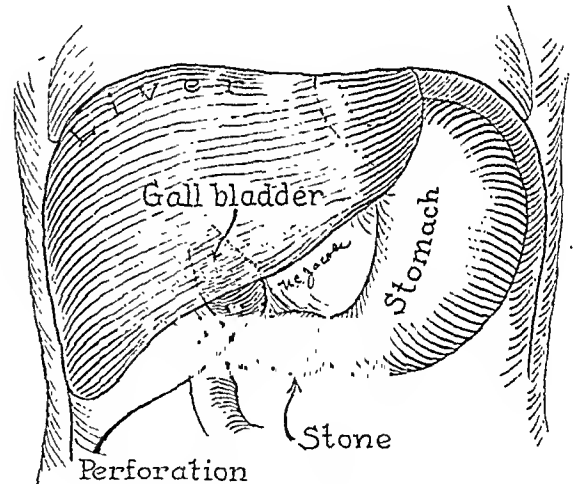


Fig. 3. Diagram shows findings present at operation.

barium then passed around this lesion, which measured about 4 cm. in diameter. The duodenal cap was not filled and the stomach was empty in four hours. The roentgenographic diagnosis was: benign type of lesion in the stomach; old duodenal ulcer (Fig. 1).

The gastro-intestinal series was repeated on October 13, 1938, with the same findings except that the observer thought that the lesion was slightly smaller in size.

Gastroscopic examination: The antral and pyloric parts of the stomach were visualized and appeared normal. A grayish-black lesion was seen in a position close to the antrum on the anterior wall near the level of the greater curvature (Fig. 2). This lesion was larger than the gastroscopic field and seemed to be free from the mucosa wherever it was visualized. The gastroscopic impression was that of a benign lesion, the exact nature of which was not known.

The patient was explored on October 14, 1938. The tumor was felt in the pyloric end of the stomach and it was at once apparent that it was a freely movable foreign body. Examination around the pyloric region revealed a gall bladder adherent on the stomach side of the pylorus (Fig. 3). The duodenum had a good deal of scar tissue

about it. A small incision was made in the stomach wall and a gall stone, about 3 cm. in diameter, was removed.

COMMENT

This is a case report of a gall stone acting as a foreign body and producing pyloric obstruction. The

gall stone had perforated from the gall bladder directly into the stomach. The perforation had become closed, allowing the gall bladder to remain adherent to the stomach wall. Apparently because of large amounts of scar tissue in the pyloric and duodenal regions, the stone was unable to pass through the pylorus. It eventually produced an intermittent pyloric obstruction.

This is probably the first report on the gastroscopic visualization of a gall stone acting as a foreign body in the stomach (2). The roentgenogram examination suggested that the lesion was located and fixed in the pyloric end of the stomach. However, the gastroscopic examination showed the body to be outside of the antrum and free from the mucosa. This apparent disagreement was probably due to the fact the gall stone was free and thus influenced by gravity and peristaltic waves. It is conceivable that food and barium with the aid of peristalsis pushed this foreign body into the pyloric end of the stomach in the attempt to pass it through the pylorus. However, in the gastroscopic position the lowest point of the stomach assumes a different level, which in some people may be at the area where this foreign body was seen with the gastroscopic.

SUMMARY

A case of gall stone acting as a foreign body in the stomach is reported. The clinical, roentgenological, gastroscopic and surgical findings are described.

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Fig. 4. Gall stone acting as foreign body. The stone was broken after its removal.

Complete Biliary Fistula of Four Years Duration With Hemorrhagic Tendency*

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WE wish to present a case of complete biliary fistula of four years duration with eventual recovery. The marked hemorrhagic tendency and prothrombin deficiency resulting from this prolonged loss of bile as well as the effects of treatment with especial reference to Vitamin K should be of interest.

M. S., a white female, age 65, was admitted to the Philadelphia General Hospital on November 9, 1938. Her complaints upon admission were (1) a draining sinus in the right upper quadrant of 4 years duration, (2) pain in the right upper quadrant, (3) stiffness of the legs of five weeks duration, and (4) purpuric spots on the extremities.

The patient was well until January, 1935, when she had an attack of right upper quadrant pain associated with jaundice, chills and constipation. She was operated upon in another hospital on February 1, 1935. A gangrenous gall bladder with bile leakage from its inferior surface

was found. The gall bladder was removed and found to contain several large stones. There was noted a large abscess on the right lobe of the liver draining from the inferior surface. The patient had a fairly smooth post-operative convalescence, except that drainage of bile through the wound continued. She was discharged on March 10, 1935.

After discharge there continued to be some jaundice and occasional chills. The patient was again hospitalized in July, 1935, with a diagnosis of biliary fistula. An X-ray following lipiodol injection was reported as showing branching shadows in the liver area interpreted as dilated hepatic ducts. At a second operation on July 24, 1935, an attempt was made to close the biliary fistula. The patient was discharged as improved on September 6, 1935. She continued to drain bile but experienced no further jaundice or chills. In November, 1937, she had rather severe bleeding from the urinary tract.

The patient was hospitalized for the third time in December, 1937, at which time there were apparently two

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Submitted July 10, 1939.



Fig. 1. Liotulol injection of biliary sinus through catheter in drainage tract.

sinus openings draining bile in the right upper quadrant. The upper sinus was injected with an opaque substance and again an X-ray showed what was believed to be dilated hepatic ducts. There was no connection apparent with the lower sinus. The patient was discharged as improved on January 22, 1938.

During the summer of 1938 she had two teeth pulled after which her gums bled for three days.

The biliary drainage from the right upper quadrant had continued from January, 1935, until her admission to the Philadelphia General Hospital November 9, 1938. Since the onset of illness the patient's weight has dropped from 186 to 126 pounds, though she states that her appetite has been good and that she has had no "indigestion" of any kind. Her stools have been clay colored since her first operation. For five weeks prior to admission, she complained of stiffness of the joints and of a dull ache in the long bones on standing. She has recently had hemorrhages from the nose and has noticed purpuric spots on the skin. Two days after admission, blood was noted in the bed pan following urination.

On admission the principal physical findings were emaciation, loose atonic dry skin, pallor of the conjunctivae, blood pressure 84/60, a scar in the right upper quadrant in which there was a sinus draining large amounts of thin yellow-green fluid, an incisional hernia in the right upper quadrant and many purpuric spots on all extremities up to several inches in diameter. The patient's stools were clay colored.

Admission studies:

Prothrombin	— less than 1% of normal.
Prothrombin Time	— 420 seconds as compared with normal of 12.5 seconds.
Blood Phosphorous	— 4.8 mgm. per cent.
R. B. C.	— 3,000,000 per cu. mm.
Blood Platelets	— 220,000 per cu. mm.
Icterus Index	— 4.0.

The prothrombin present on this and subsequent determinations was calculated according to the method of Quick (1) and his associates. This method depends upon the clotting time of recalcified plasma to which thromboplastin has been added. The graph constructed by Quick from which prothrombin per cent may be calculated has been used, each determination being done in triplicate, using a normal control.

The administration of alfalfa extract (Vitamin K) was begun at 200 cc. per day with sodium choleate grains five,

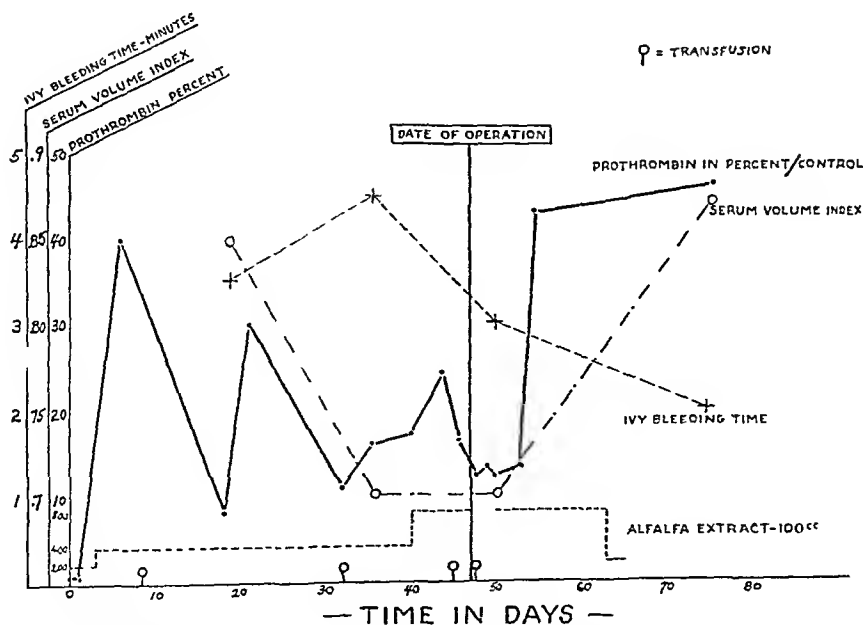


Fig. 2. Graph showing prothrombin per cent, Serum Volume Index and Ivy bleed-



Fig. 3. Outline of biliary tract by barium meal three months after choledochoduodenal anastomosis.

twice a day. The alfalfa extract was prepared by extraction of dried alfalfa with acetone in a Soxhlet apparatus for six to eight hours. After extraction the acetone was distilled off and the residue suspended in water. Each 200 cc. of the "Tea" represents the extraction from forty grams of dried alfalfa.

On 11-13-38 the dosage of alfalfa extract was increased to 400 cc. per day and three days later the prothrombin was 40% of control. A transfusion of 600 cc. of citrated blood was given on 11-17-38.

On 11-19-38 the patient was transferred to the Surgical Ward.

The lipiodol X-ray study on 11-21-38 was reported as showing an oval-shaped shadow approximately 1 by 4 cm. in size at the level of the 12th rib. This was interpreted as being dilated common duct. There were two or three smaller branching shadows believed to be biliary radicals or sinuses (Fig. 1).

In further studying the bleeding tendency presented by this patient it was thought that it would be of interest to observe any changes in the Ivy (2) bleeding time and in the Serum Volume Index of Boyce and McFetridge (3) and to compare these findings with the prothrombin levels. The Ivy bleeding test consists simply in observing the period of bleeding from a skin puncture while a tourniquet with a pressure of 40 mm. of mercury is in place. Any bleeding of four minutes or longer is considered a definite indication of hemorrhagic tendency.

The Serum Volume Test is a measure of clot retractility. Three cc. of blood is placed in a calibrated tube and allowed to stand at room temperature for four hours. The clot is then removed. The volume of serum remaining over one-half of the blood volume equals the index. An index

of one is normal, any reading below this being considered as progressively indicative of a tendency to hemorrhage.

The results of those comparative observations may be seen in the graph (Fig. 2).

Examination of the bile on 11-29-38 revealed: chlorides 675 mgm. per cent; eholate, 61 mgm. per cc.

On 12-12-38 the patient received a transfusion of 250 cc. of citrated blood.

On 12-20-38 the dosage of alfalfa extract was increased to 800 cc. per day with sodium eholate grains five, four times a day.

On 12-24-38 a transfusion of 200 cc. of citrated blood was given.

On 12-27-38 a choledochoduodenostomy was performed by Dr. Ferguson under local anesthesia, a number 14 catheter being placed in the original sinus tract and one Penrose drain in the operative site. The patient received a transfusion immediately after operation. She was given nothing by mouth for forty-eight hours postoperatively, fluid intake being maintained intravenously.

On 12-29-38 the patient was again started on 800 cc. of alfalfa extract daily with sodium eholate grains five, four times a day.

On the third postoperative day the dressings were soaked with bile and the catheter in the original sinus was loose. On the fifth postoperative day the light color of the drainage and some skin irritation raised the question of duodenal fistula. The patient's stools during this time remained brown, however, and by the twelfth postoperative day drainage through the wound had ceased.

The administration of alfalfa extract was stopped on 1-13-39 and the following day the patient was allowed out of bed. There had been no evidence of any hemorrhage postoperatively.

During her stay in the hospital the patient's hemoglobin had maintained a level of about 13 grams per 100 cc. The cholesterol ranged between 122 and 258, the esters usually approximating 50%. The Icterus Index ranged from four to 12.

On 1-25-39 a gastro-intestinal X-ray showed no deformity of the stomach or duodenum. On reaching the duodenum, the barium ascended rapidly into the biliary tract, outlining one large duct and two smaller ones (Fig. 3).

On 1-27-39 the patient was discharged to her family, having no abdominal or gastro-intestinal complaints, but still experiencing some difficulty in walking.

She was seen in follow-up clinic on 2-12-39. The wound was well healed and there had been no drainage. However, she still had some difficulty in walking. When seen again on 3-12-39 she was without complaint, her appetite was good and her ability to walk much improved.

On 3-29-39 Ivy bleeding time was 2½ minutes.

Prothrombin	— 58% of control
Serum Volume Index	— .8
Icterus Index	— 3
Serum Protein	— 6.5

DISCUSSION

This patient's course in the hospital presents several features of interest. She had total biliary drainage for a period of approximately four years with late but repeated bleeding manifested as urinary bleeding, bleeding from the gums, purpuric spots and joint involvement. In association with this hemorrhagic tendency our admission studies showed a very low prothrombin, less than 1 per cent, probably one of the lowest reported.

We should like to call attention to the variable effect of Vitamin K and bile salts on the blood prothrombin level in this patient. As may be seen from the graph, the determinations showed quite a marked shifting in

the prothrombin level from time to time in spite of a constantly increasing dosage of alfalfa extract and bile salts.

It may be noted that the immediate response to the administration of Vitamin K and bile salts was extremely favorable, the prothrombin rising from 1% to 40% of normal in five days. Thereafter, there was an abrupt fall never reaching the above figure until after surgical anastomosis between the duct and the duodenum. One might question the results of the test for prothrombin if the variations did not coincide very well with those noted in the Ivy bleeding time and the Serum Volume Index of Boyce and McFetridge. Certain it is that the maximum time for surgical intervention as measured by the prothrombin content of the blood came during the first week or two after the administration of Vitamin K and bile salts.

There is also shown on the graph the relationship between the Serum Volume Index and the Ivy bleeding time to the prothrombin per cent. These simple tests, the performance of which requires no elaborate equipment or special laboratory facilities, gave results rather closely paralleling the variations in prothrombin level. We believe these tests to be of value in determining the presence of a tendency to hemorrhage particularly in any circumstance where the

laboratory facilities for determination of blood prothrombin levels are not available.

This case also demonstrates the feasibility of the use of local anesthesia for major abdominal procedures in these desperately ill patients. Local infiltration with one per cent novocaine preceded by adequate preoperative sedation proved to be perfectly satisfactory for this operation.

As may be seen from the graph, the operation was performed in the face of a low prothrombin level. This was done because we believed that the patient was losing ground in spite of constant feedings of the alfalfa extract. There was no postoperative bleeding. This may be attributed in part to the use of transfusions, though Snell, Butt and Osterberg (4) believe the effect of transfusion in raising the blood level of prothrombin is transitory. The patient received four transfusions in all, one of which was three days before operation and one immediately following it.

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Carcinoid Tumors of the Small Intestine

By

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IN 1888 Lubarsch (1) described two cases of small intestinal neoplasms situated in the submucosa. These differed from the ordinary adenocarcinomata. He studied these tumors in serial sections and found that they were connected with the crypts of Lüberkuhn. While these tumors showed lack of metastases, absence of true glandular structure and were composed of cells unlike those of normal intestinal mucosa, he still classified them as primary carcinomata of the ileum.

Ranson (2) described a similar tumor, which however extended into the mesentery and through the peritoneal coat, and was accompanied by secondary tumors in the liver, whose structure was the same as that of the primary growth. He too considered this neoplasm as belonging to the category of carcinoma. Oberndorfer (3) was the first to recognize definitely that this tumor was not a true carcinoma and called it carcinoid. He considered it to be quite harmless in character and maintained that it originated from pancreatic rests. Burkhardt (4) analyzed a group of small intestine tumors of similar type, and came to the conclusion that they were definitely derived from the intestinal epithelium and had a low degree of malignancy. Forbus (5) in an analytical review of the various theories of development, supports the endocrine theory and calls them endocrine tumors or

argentaffine tumors and maintains that they are separate and distinct from the carcinomata. In his conclusion he calls attention to the "general harmless character of the argentaffine tumors." Gaspari (6) reports a similar type of tumor but classifies it as carcinoma. Very recently Wyatt (7) again reviewed this subject, reporting three cases—two in the appendix and one in the caecum. He concludes that "this tumor is a carcinoma arising from the Kulschitzky cells of the intestinal epithelium" and "that all carcinoids are slow growing but malignant tumors." Humphreys (8) collected 152 cases of argentaffine tumor of the small intestine and found that 24.4% of them had metastasized.

Raiford (9) analyzed 29 of his own cases and found that 6 of them—over 20%—were malignant.

TABLE I

Location	Total Number	Malignant	Per Cent
Stomach	1	1	100
Small Intestine	9	2	22
Appendix	17	1	5.9
Large bowel	2	2	100

In his description of the histogenesis of this neoplasm Raiford writes that "these peculiar cells were first described by Nicolas Kulschitzky (10) in 1897,

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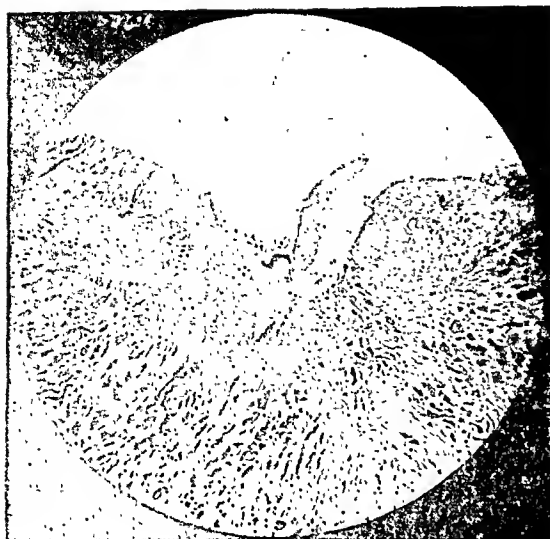


Fig. 1

as specialized epithelial cells having a characteristic structure." Schmidt restudied them in 1905 and noting their yellow color called them "gelber zellen." He concluded that they were a part of the chromaffin system and similar to the cells of the adrenal medulla. Gosset and Masson (13) found in 1914 that certain granules in the cytoplasm had the power of reducing silver compounds, having brown or black particles. In view of this affinity for silver, they called the cells "argentaffine." By subsequent investigators they have been called "entero-chromaffin cells" (Ciaccio) (11) and "chromo-argentaffine cells" (Cordier) (12).

The cells are found in all parts of the intestinal tract of men and many of the higher vertebrates. They differ in number with the location, being most numerous in the appendix and terminal ileum, where from five to ten may be found in each crypt. They are less common in the colon and upper small intestine and comparatively rare in the stomach and rectum. They are concentrated at the bases of the crypts, where they are pear shaped, with broad bases lying on the basement membrane and narrow bottle shaped necks leading up to the lumen of the crypt. The cytoplasm stains lighter than that of other epithelial cells, but scattered throughout are numerous acidophilic granules. The nucleus is round, uniform in size, and located near the center of the cell. It contains a finely reticulated network with numerous small chromatin particles. Stained by the silver impregnation technic of Gossett and Masson, the cytoplasmic granules appear as tiny brown or black particles.

The origin of the cells is still a moot question. Masson on the basis of their appearance in regenerating epithelium and their occasional occurrence in malignant tumors arising from the epithelial cells, attempts to explain them as differential epithelial cells of ectodermal origin. Kull, studying them in the chicken embryo concluded that they were of mesenchymal origin. It seemed to Raiford that they are cells of ectodermal origin which have migrated early in life from the neural crest and become adapted to a special function in forming a part of the general

chromaffin system. In favor of this mode of origin is the striking similarity of the cells of certain tumors to the cells of the adrenal gland, not only in morphological form but also in the gross color of the tumor. The affinity for silver exhibited by tumor cells is not present in epithelial cells, but is possessed by many cells of ectodermal origin. As has already been pointed out, the appearance of rosettes in typical carcinoids links them to the neuro-blastomas.

The function of the cells is likewise unknown. Masson regards them as forming a diffuse endocrine organ and through secretion of a substance which he designates as "neurocine," exerting a regulatory influence upon the proliferation of smooth muscle fibers of the intestinal wall, especially those of the muscularis mucosa. By this he explains the smooth muscle hypertrophy coincident to the carcinoid tumors, especially those located in the appendix.

There remains the correlation of these normal argentaffine cells with the carcinoid tumors. That these tumors arise from these cells is generally conceded. The similarity in both staining reaction and microchemical properties gives striking evidence of their relation. It is also occasionally possible to observe the growth of a tumor directly from the cells in the crypts.

Masson contends that the normal cells migrate first to nerves of the submucous plexus, where they may normally be found within the substance of the nerve. In this location, proliferation forms neuromata, and these in turn are directly responsible for subsequent tumor formation. One occasionally does find a neurogenic hypertrophy coincident with carcinoid formation and it is true there are cells in proximity to the nerves which strikingly resemble tumor cells. They are possessed however of a perineural and not an intraneural arrangement and I am not convinced that they signify more than a secondary invasion of the nerve sheath. Therefore while there is excellent reason to believe that the tumors arise from the normal argentaffine cells, the presence of argentaffine neuromata as intermediary stages must be questioned.

To summarize, it is ascertained beyond reasonable doubt that the carcinoid tumors arise from the cells of Kulschitzky or the chromoargentaffine cells of Masson and that these cells are normally present in the intestinal tract of man. They are thought to be chromaffin in nature, and the tumors are consequently chromaffin tumors."

In view of the rarity of this condition and in view especially of the lack of unanimity regarding its character, it is worth while reporting these cases until sufficient data are accumulated to put this subject on a firm basis.

A. S., a woman of thirty-seven, was admitted to Beth Israel Hospital on January 28, 1938. Twelve weeks prior to this date she had begun to feel transient pains in the upper abdomen radiating to the right lower quadrant. These lasted from ten to thirty seconds, and while they were present, a mass about the size of an orange would appear to the right of the navel. Obviously a loop of bowel was contracting powerfully against an obstruction.

Occasionally the woman vomited, and as time passed the attacks of pain became more frequent. Constipation developed. Appetite disappeared, and there was a loss of 45 pounds in weight.

A diagnosis was made of intestinal obstruction, and the patient was operated on. Part of the small bowel was found then to be distended to three times the normal calibre and tracing it down obstruction was found at a place where there was a hard annular constriction. About 5 cm. distal to this point there was a small induration about 1 cm. in diameter in the wall of the small bowel. An entero-anastomosis was made, and a month later, at a second operation, the growth was resected. The pathologist reported that there were two carcinoid tumors of the jejunum, one of them causing the stenosis. There was some ulceration of the mucosa over both of them. The

patient recovered uneventfully. Fig. 1 shows the microscopic appearance of the section of the tumor.

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Editorials

SPECIAL NOTICE

THE current issue of the Journal will constitute the last number of Volume VI. The first issue of Volume VII will appear early in January and from then henceforth each volume will begin with the January issue. This will result in Volume VI being a ten issue volume. The change has been considered advisable by the Editorial Council to avoid the confusion which naturally arises when the volumes do not coincide with the calendar month. This change will make no difference to subscribers whose payments will entitle them to twelve issues.

THE LIMIT IN THE TREATMENT OF ULCER

THE last drug that any physician would ever think of using in the treatment of peptic ulcer would probably be histamine. For this reason it is interesting to find in the *Presse Médicale* for February 9, 1938, a report by Jacob and Israel to the effect that they have been getting good results in the treatment of the painful crises of ulcer by giving daily injections of 0.1 mg. of histamine. The authors started this treatment on the hunch that the good results obtained with histidine were due to the presence of histamine as a contaminant! They reported that in all the cases in which the patients were treated the pain stopped, and they concluded that this may have been due to vasodilatory effects, relaxation of smooth muscle, or to some antalgic power resident in the histamine.

We hate to suggest this because there are so many persons about with a fondness for trying new things and then writing them up enthusiastically, but really, shouldn't someone now try, at least once, to treat ulcer with a mixture of equal parts of tabasco sauce, cucumber juice, absolute alcohol and carpet tacks?

Walter C. Alvarez, Rochester, Minn.

SOME PECULIAR TRENDS IN THE INCIDENCE OF PEPTIC ULCER THROUGH THE YEARS

EVERYONE who is at all interested in the problems of peptic ulcer will want to read Alsted's little book on the changing incidence of peptic ulcer as is shown by statistics gathered through the years in the hospitals of Copenhagen. Students of the subject are well aware of the fact that years ago peptic ulcers were thought to be present almost always in the stomach and seldom in the duodenum. In Denmark, as in the United States, the ratio of duodenal to gastric ulcers has risen from about 1 to 1 to 10 or more to 1.

Doubtless much of the change of opinion which came about 1905 was due to the discovery by surgeons that duodenal ulcer was a common lesion. Actually, the pathologists did not come to realize how frequently the duodenum is scarred until Robertson and Hargis called attention to the remarkable shortening of the distance from the pylorus to the papilla of Vater which is found in every case of healed duodenal ulcer. But one can hardly ascribe all of the differences between the old and the new statistics to a defect in observation. Furthermore, although it is highly probable that much of the recent increase in the incidence of duodenal ulcer which shows up in the records of hospitals and clinics can be ascribed to the increasing frequency with which patients with indigestion are studied by roentgenologists, it is doubtful if all the increase can be explained in this way. Besides, improvements in diagnostic skill could hardly account for the marked change in the sex incidences of the two types of ulcer which has been observed in almost all countries where statistics have been gathered. Thus, during the last forty years in Denmark, the ratio of men to women with ulcer has risen from about 1 to 1 to 3 to 1.

One of the interesting points made by Alsted is that it appears that years ago ulcers were generally acute and when they healed the patient commonly remained well. Today ulcer is usually looked on as a chronic disease which will probably recur many times throughout a lifetime. One must suspect, however, that much of this difference in the aspect of the disease is artificial and due only to the change in the attitude of physicians which came with experience. Some men will remember that around 1920 many of the older gastro-enterologists and surgeons found it hard to face the fact that ulcer is a chronic disease and that the patients do not always stay well after either medical or surgical treatment. Even in the field of science, when a man hates to face a new and unwelcome fact he can often do a very thorough job of closing his eyes and mind to it.

One of the most puzzling features of Alsted's data is the decided break in the curves at a point which corresponds to the period at the end of the World War. If we could only understand what happened then to so suddenly and markedly change the incidence of hematemesis we might have a very useful therapeutic hint at our disposal.

It should alarm everyone to see how steeply the curve which represents the incidence of gastro-in-

testinal hemorrhage in men has been rising during the last few years. It is remarkable also to see how the incidence of ulcer in the case of men is rising rapidly along a straight line, while it is rising but slightly if at all in the case of women.

Walter C. Alvarez, Rochester, Minn.

NEW BOOKS ON THE EARLY DIAGNOSIS OF CANCER OF THE STOMACH

ALL gastro-enterologists will rejoice in the recent appearance of two fine books in which the authors stress the importance of studying and learning to recognize the earliest stages and appearances of cancer of the stomach. For years the textbook description of cancer of the stomach was that of the final hopeless stage with emaciation, coffee-ground vomitus, complete achlorhydria and a palpable tumor, and eventually physicians became so used to and so satisfied with this picture as to resent the writings of anyone who dared describe the picture of early cancer of the stomach as it appears in strong, healthy-looking men who complain of only a little hunger pain, or loss of appetite or strength, and who have a normal gastric acidity. When such descriptions were noticed or quoted at all, about all that was said about the writer was that he was an untrustworthy fellow who was bent on calling all sorts of lesions cancerous when they were really nothing of the sort.

Now there comes out of Germany Konjetzny's beautifully illustrated book in which the early stages of the various types of carcinoma of the stomach are described, and the work of men all over the world who have described early carcinoma of the stomach is recognized and quoted. Konjetzny writes largely from the point of view of the pathologist, and most of his illustrations show the histologic structure of gastric carcinomas of the several types. As one would expect, approximately half of the book is taken up with a discussion of conditions which are probably precancerous.

The other interesting book which is well worthy of notice here is that of René Gutmann and his associates. This book is written largely from the points of view of the clinician and the roentgenologist. Gutmann, Bertrand and Péristiany have for years been studying the early radiologic signs of cancer of the stomach, and it is a pleasure to find them admitting now that in many cases it is impossible for the roentgenologist to distinguish between a benign and a malignant ulcer. Gutmann has written a very interesting chapter on the several puzzling syndromes by which cancer of the stomach commonly announces itself. Unfortunately for our patients, those of us physicians who received our medical training thirty years ago were never told that the first sign of cancer of the stomach is often constipation, hunger pain, a little nausea, some heartburn, anemia, or loss of energy or appetite.

Submitted September 1, 1939.

Walter C. Alvarez, Rochester, Minn.

THE SIGNIFICANCE OF DUODENAL STASIS

DURING the years many articles have appeared on duodenal stasis, on the symptoms supposed to be produced by it, and on the way they can be relieved by duodenojejunostomy. Some time ago Wilkie of Scotland, was an enthusiastic advocate of this operation,

but as years passed and he saw many of his patients returning with the same old symptoms, he lost interest in the subject. Unfortunately, in most cases, the man who makes an enthusiastic preliminary report about a few apparently cured patients fails to write anything later when the patients begin to come back with the same old pains and troubles.

For fifteen years the writer has hunted for a good typical case of duodenal stasis, curable by operation, but so far has not found one. Occasionally it seemed as if one had been found, but then further roentgenologic studies showed that the stasis was not repeatedly demonstrable. The writer has seen only a very few cases in which the operation was done by the home surgeon, and then the results were not encouraging. In some of these cases it became clear with the passage of time that the syndrome had really been due to a migraine in which the headache was so mild and the abdominal storm so great that it is no wonder that the correct diagnosis was missed.

In a recent paper in the April, 1939, number of "Annals of Surgery," Oppenheimer, of Beirut, reported a series of cases in which some duodenal stasis could at times be demonstrated. His studies led him to doubt the importance of pressure by the mesenteric artery on the jejunum as a cause of duodenal stasis. Neither did he find that stasis is caused commonly by adhesions, kinking, or intrinsic or extrinsic growths. Interestingly, duodenal stasis was found in students who presented none of the symptoms which are supposed to be typical of duodenal stasis, and it was not found in some cases in which the typical symptoms were complained of.

Accordingly, Oppenheimer concluded that duodenal stasis, as demonstrated roentgenographically, does not necessarily indicate anatomic obstruction, and it does not mean that the indigestion complained of is due to the peculiarity in function found.

All of this does not mean that there is no such thing as duodenal stasis with symptoms. All it suggests is that no duodenojejunostomy should be performed until repeated studies have shown that the stasis is often present and that the symptoms are not those of an atypical migraine or of a neurosis in a constitutionally inadequate person.

Walter C. Alvarez, Rochester, Minn.

THE NEW OXYGEN TREATMENT FOR MIGRAINE

IT was recently reported in the Proceedings of the Staff Meetings of The Mayo Clinic (March 15, 1939) that the administration of pure oxygen for one or two hours will, in some patients with migraine, abort the attack. The discovery was made by a layman, Mr. Charles E. Rhein, of Chicago. Further experience by Alvarez and Boothby and the reports of physicians throughout the country now leave no doubt as to the ability of this treatment to bring grateful relief to a considerable number of the sufferers with this miserable and disabling and common disease. Just how large the percentage of patients is who can be helped in this way is as yet unknown.

Curiously, cases have been found in which one headache was promptly relieved by oxygen and another, a few days later, was not. An effort must now be made to find out why some persons respond well and others do not. The impression gained is that the patients

who do not respond well are those whose migraine is atypical or complicated by other diseases such as hypertension, or by a considerable degree of psychopathy or the nervous storms of the menopause.

Experiments on animals have shown that a better oxygenation of the tissues of the brain up to a certain limit will lower the tendency to convulsive seizures, and some evidence is accumulating to show that epilepsy also can be helped by a better oxidation of the brain.

Before permitting a patient to lay out considerable money for equipment, the physician will do well first to see if he or she responds well to the inhalation of oxygen. This may be done by having the patient breathe oxygen from a small basal metabolism machine or from the anesthetist's equipment in a hospital. In the larger cities the companies that sell oxygen will often rent the necessary apparatus for a time until the patient is sure he wants to buy. If good results are secured, then the patient can buy a BLB mask (sold by the Ohio Chemical and Manufacturing Company, of Cleveland, Ohio) and can secure a tank of oxygen with a reducing valve and perhaps a flowmeter. A flow of 6 liters a minute is usually about right. The little bag on the BLB mask should about collapse with each breath. The valves on the tube between the mask and the rebreathing bag should be closed.

There need be no fear about breathing pure oxygen for a couple of hours, even two or three times a day. Especially in those bad cases in which the patient goes from one headache into another, the oxygen treatment is often better than is that with ergotamine. There

are no uncomfortable by-effects, the relief comes more quickly, and there need be no fear of injury to arteries. Interestingly, in several such bad cases, there has been a marked lessening in the severity of the attacks and in the frequency with which they recurred. This may well have been due to the fact that the patient got rest which was impossible when she was going from one horrible attack into another.

The patient should not be discouraged if the first treatment does not bring prompt and complete relief. Sometimes, at first, the brain is so irritable and tired that no treatment could put an immediate stop to the headache. Then a suppository of 3 grains (0.2 gm.) of nembutal may help greatly by quieting the vomiting center and giving the patient sleep and rest. It is useless to give drugs by mouth when nausea is present. In some bad cases intramuscular injections of gynergen will get the patient into a better condition, and then perhaps the oxygen treatment will work well. There is no known reason why the two treatments should not be used together at first. One patient who, on one day, failed to get relief from oxygen inhalation for two hours, later, when she was not so tired, obtained perfect relief in half an hour. In some of the severe cases the patient who gets relief after breathing oxygen for an hour may start to slip back after an hour or two. Then, often, another hour's treatment will put an end to the attack.

One splendid feature of the oxygen treatment is that commonly the patient comes out of the attack with a clear head and able to go right back to work.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

The Wisdom of the Body. By Walter B. Cannon, New York, W. W. Norton & Company, Inc., 333 pp. Price \$3.50.

THIS is a revised edition of one of Cannon's thought producing and valuable books. One of the most remarkable things about living organisms is their ability to get back on an even keel after something rocks the boat. In this book one learns why the body is able to maintain a fairly constant supply of water, salt, sugar, proteins and fat. We learn something about the maintenance of a constant temperature and about the defenses against injurious agents. We learn something also about the ways in which the body repairs itself after illness or injury, about the value of antitoxins in disease and the ways in which the glands and the nervous system contribute to the stability of the several bodily functions.

This is a book which is of great interest not only to the professional physiologists but to the physician and even to the scientifically inclined layman. We recommend it heartily.

The Canned Food Reference Manual. New York, American Can Company, printed by The Haddon Craftsmen, Inc., 242 pp.

THIS is a splendid little book crammed with information, well written, well printed, and well illustrated. Every dietitian should have a copy on the desk. The book is full of tables giving the composition of

large numbers of canned foods, together with the content of vitamins and the more important chemical elements.

Der Magenschleim. By Arthur Mahlo, Stuttgart, Ferdinand Enke, 53 pp., 1938. Price RM 2.40.

THIS is a monograph of 53 pages on the mucus of the stomach. Much information has been gleaned from the literature, and there are brief comments on some of the author's own researches. The little monograph should be of interest to all those who have been studying the several components of gastric secretion. We have the feeling that it would have been much better if while Dr. Mahlo was at it he had gone into his subject in more detail and had presented more laboratory data. However, this booklet will be a great help to anyone trying to become oriented in this field.

Vitamin-Mineral Digest. Compiled by the Scientific Staff of the U. S. Vitamin Corporation under the guidance of Dr. Casimir Funk and Dr. Harry E. Dubin, 40 pp., 1939.

THIS booklet, published by the United States Vitamin Corporation of 250 East 43rd Street, New York, was written by Dr. Casimir Funk and Dr. Harry Dubin. Everyone knows that Dr. Funk was the man who originated the term "vitamine." In recent years the "e" has been removed so as not to confuse these

curious chemical substances with the amines. Following the question and answer style, this little book gives a great deal of information which the physician will occasionally want to have and which might take him some time to dig out of a larger volume or out of the current literature.

Physiology of the Nervous System. By J. F. Fulton. New York, Oxford University Press, 675 pp., 1938.

THIS is a splendid book and one that is much needed today. In the past, books on the nervous system have been written either from the point of view of the anatomist, or from that of the neurologist and the neurosurgeon. Now we have a book written from the point of view of a physiologist. Here Fulton brings together and summarizes an enormous amount of work which has been done during recent years on the problems of the structure and function of the nervous system. Much of this work is as yet unheard of by general practitioners and almost unknown to internists. Much of it has been done in research laboratories with apparatus borrowed from the physicist, and much of it has been done on animals in which various parts of the brain have been removed.

The part that will particularly interest the gastro-enterologist will be the chapters on the autonomic division of the nervous system and on the hypothalamus with its centers for the regulation of the autonomic nervous system. It is unfortunate that during the last twenty years so much of the theorizing about the sympathetic and the parasympathetic nerves that has encumbered the literature has been done by clinicians who had only the vaguest idea of what they were talking about. One has to wonder often if they knew what the sympathetic and the parasympathetic nerves are or how they work. In most cases the writer's stock of information had apparently been that carried over from college days and from textbooks that saw the light some thirty years ago.

Of late the conception of autonomic action has been greatly changed by the discovery that out of the ends of these nerves come chemical substances which profoundly affect not only smooth muscle and other tissues but also the consciousness of the individual. Much information is being gathered also on the important subject of the relation of the autonomic nervous system to the transmission of pain, and especially of the type of pain that brings much worry to the internist.

Any clinician who will read Fulton's Chapter 13 on the hypothalamus must, we believe, be greatly impressed with the probability that some of the curious distresses which so alarm nervous and psychopathic persons are the result of disturbances in the functions of the hypothalamus. This is the place in which highly organized vegetative functions are integrated. By stimulating this region one can produce marked sweating, vasoconstriction, or changes in blood pressure throughout the body. By injury to this region, one can produce changes in body temperature, changes in the level of blood sugar, changes in blood pressure, in water balance, in the metabolism of carbohydrates and fats, and in sexual development. It is a remarkable fact shown particularly by Bard that when cerebral control is removed from this hypothalamic region, the animals will exhibit outbursts of fear or rage during which the pupils dilate, the hair stands on end, the

heart rate increases, blood pressure rises and salivation occurs. Obviously some sort of a storm takes place in the autonomic nervous system. Some experimenters have shown that these animals develop also extrasystoles and other disturbances of cardiac function.

It is interesting also that barbituric acid and anesthetics greatly affect these nuclei. The gastro-enterologist must be greatly interested in this region because stimulation of these centers will markedly affect the motor and secretory functions of the stomach and intestine. It is known also that injury in this region will give rise to ulceration of the stomach and duodenum.

Already it is possible to recognize five distinct syndromes arising in the hypothalamus, four due to destruction of areas and one due to periodic irritation of the centers. These syndromes are (1) hyperthermia, (2) diabetes insipidus and emaciation, (3) the adiposogenital syndrome, (4) hypersomnia with disturbed thermal regulation and (5) autonomic epilepsy. Today it is known that diabetes insipidus is produced by a certain lesion of the anterior nuclei of the hypothalamus. Similarly, the work of Philip Smith and others has shown that one type of the adiposogenital syndrome is produced by disease in the middle group of hypothalamic nuclei. As one would expect then, patients with this type of trouble can not be much helped by the injection of pituitary substance.

The clinician must be greatly interested in this region also because it has so much to do with disturbances of sleep and with the reaction of the patient to barbiturates. As one might expect, it is this part of the brain which is particularly involved in many cases of encephalitis. There is some center in this region of the hypothalamus which suppresses cortical activity and gives rise to epileptoid spells.

The State of California, a Medico-Geographical Account. By J. Praslow. Translated from the German by Frederick Cordes. John J. Newbegin, San Francisco, 86 pp., 1939.

THIS is an interesting little book. It is naturally of particular interest to Californians, but any physician who is interested in history and exploration will find it good reading. Five years ago Dr. Cordes happened to note in a catalogue of rare books a title which interested him. He sent for the little volume and soon was busy translating it into English and learning all he could about the author, who practiced medicine in San Francisco from 1849 to 1856. After a trip back to Germany he went to Culiacan on the west coast of Mexico and practiced there until his death.

The book gives much interesting information about the appearance of California in the early days, about the Indians and the miners, and about the bad health conditions due to poor food and water. When Dr. Praslow arrived in San Francisco he found some fifteen or twenty physicians already there. There were no pharmacies at first, and every doctor had to dispense.

Praslow was much interested in the ever-present problem of scurvy. Ships coming around the Horn were generally full of it, and on landing, the patients were given large amounts of meat, many vegetables, dried fruits, and solutions of vinegar. Tartaric, citric,

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sulphuric and muriatic acids were given, also scurvy grass. The best remedy proved to be potatoes, scraped and eaten raw or applied as poultices over the swellings and ulcers. Brewer's yeast was also used.

In San Francisco there were severe epidemics of dysentery and diarrhea and at times probably cholera. Miners who went up through the swampy central valleys suffered severely with malaria. Typhoid fever was also a problem. Great numbers of Chinese were brought in from the Orient, carrying their diseases with them. Their prostitutes brought a particularly virulent type of syphilis and gonorrhea.

It is interesting to note that the Indians of the Sacramento Valley were much troubled with malaria. One wonders if they had it before the whites came.

According to Praslow, cretinism was rather common among the Indians and native-born Spaniards, especially in the neighborhood of Cape Mendocino. Interestingly, this region is still an endemic focus of thyroid disease.

Tuberculose de Tube Digestif. By André Cade, Paul Santy and Jean Heitz, Paris, G. Doin & Cie., 411 pp., 1937. Price 80 Fr.

This is an excellent monograph on

tuberculosis of the digestive tract, well written and well illustrated. There is a large bibliography. It is probable that some of the lesions described under tuberculosis of the terminal ileum fall in the group of troubles now known as terminal ileitis. This book is well worthy of a place in the library of the gastroenterologist.

Abstracts

FRIEDMAN, M. H. F.

Gastric Secretion in Birds. J. Cell. and Comp. Physiol., 13:219-234, April, 1939.

In pigeons and chickens under Nembutal anesthesia gastric secretion is intermittent, not spontaneous or continuous. In both the pigeon and the chicken the secretion of acid and of pepsin is under the control of the parasympathetic nervous system. In birds, histamine stimulates chiefly the secretion of acid, the gastric juice being extremely poor in pepsin. The concentration of pepsin is higher in the gastric juice of the chicken than in that of the pigeon. The rate of gastric secretion is dependent on the volume of body fluids in the circulation. Repeated injections of large doses of histamine cause hemorrhagic lesions of the proventriculus in the form of multiple erosions.

W. C. Alvarez, Rochester, Minn.

WEINSTEIN, LOUIS AND BOGIN, MAXWELL.

The Effect of Banana Feeding on the Intestinal Flora and on Constipation in Children and Adults. Rev. Gastroent., 6(1):12-21, 1939.

Studies were made on persons having predominating *E. coli* but no *L. acidophilus* in the feces and whose constipation did not respond to ordinary therapeutic measures. Diet was unchanged except for the addition of 3-4 ripe bananas a day. *L. acidophilus* appeared after the first week. By the end of the second week it constituted 90-95 per cent of the flora in some cases. After the sixth week it had disappeared in all but one person. Constipation was completely relieved in 1-2 weeks.—G. H. C. (courtesy of Biological Abstracts).

SNYDER, C. D., JOHNSON, R. E. AND PEEK, C. MCI.

The Minute-Volume Uptake and Output of Substances Perfused Through Liver Surviving in an Omeometer. Am. J. Physiol., 124(3):704-716, 1938.

Analyses of the inflow and outflow to a liver preparation surviving in an omeometer have been made for K,



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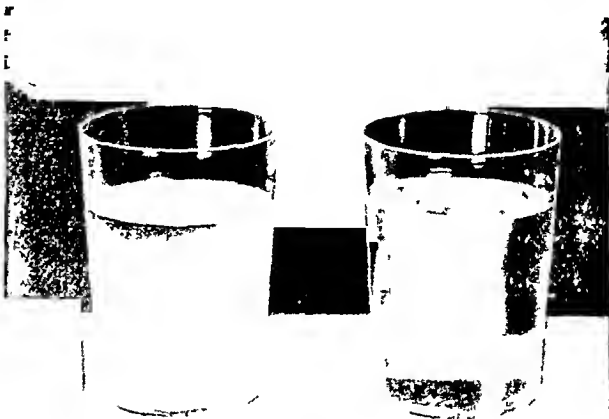


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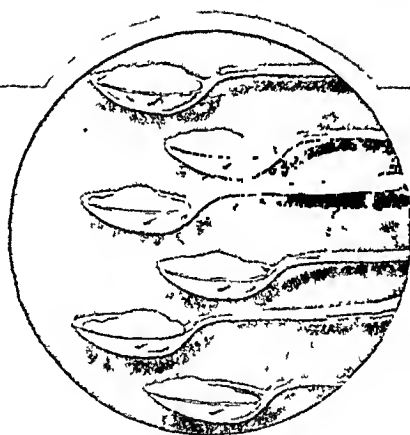
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sugar nad, in a few experiments, also for chloride. The samples analyzed were collected from the hepatic outflow at frequent, successive and short-lasting intervals of time while the organ was responding to injections of acetyl-B-methylcholine chloride or adrenalin chloride into its inflow cannula. When the changes in volume of the organ as well as changes in rate of outflow and inflow are taken into the calculations, then the amounts of uptake and output of substances contained in the perfusate may be quite different from those indicated by concentrations alone at the sites of inflow and outflow. The differences in

content per unit of time under certain conditions may be all out of proportion to the differences in content per unit of volume, and the values for the former may change greatly while those for the latter change not at all and vice versa. The method obviates resort of the procedure employed in chronic cases, namely, the taking of sections out of the organ under investigation. The method further makes possible the exptl. differentiation between the vascular and glandular effects of various agents upon the liver. The experiments here reported demonstrate this differentiating capacity of the method, especially when

autonomonametic agents are injected into the portal vein of the liver. The method promises further to be useful both in the study of the role played by an organ in producing transient alterations in the composition of the general circulation (minute-volume output here is of the greatest importance); and in the study of the role played by the varying contents of the general circulation, or of affluent nutritive fluids, upon the organ itself in both its vascular and glandular responses.—Author (courtesy of Biological Abstracts).

WINDLE, W. F. AND BISHOP, C. L.

Prenatal Intestinal Movements in Anorexia. Proc. Soc. Exp. Biol. and Med., 40(1):2-4, 1939.

Gastro-intestinal movements were observed in fetuses delivered by experimental Caesarian section without anesthesia and with placental circulation intact in cats previously decerebrated. Propagation peristalsis occurred when the umbilical vein blood was less than half saturated with oxygen. Marked anoxia led to rhythmical segmentation. Profound asphyxia resulted in pendulous writhing of intestinal loops with loss of tonus.—Authors (courtesy of Biological Abstracts).

BURNSTEIN, C. L.

Effect of Some Short-Acting Barbituric Acid Derivatives on Intestinal Activity in Vivo. Proc. Soc. Exp. Biol. and Med., 40(1): 122-124, 1939.

The action on intestinal activity of some of the barbituric acid derivatives most commonly employed for intravenous anesthesia (evipal, pentothal, nembutal, amytal and sodium thiethylamyl) was studied in dogs with Thiry-Vella fistulas of the jejunum. After a transitory immediate effect (5 to 15 minutes) characterized by depression of rhythmic intestinal contractions and tonus there followed a more prolonged period (10 minutes to 2 hours) in which the intestinal contractions and tonus were increased markedly above normal.—C. L. B. (courtesy of Biological Abstracts).

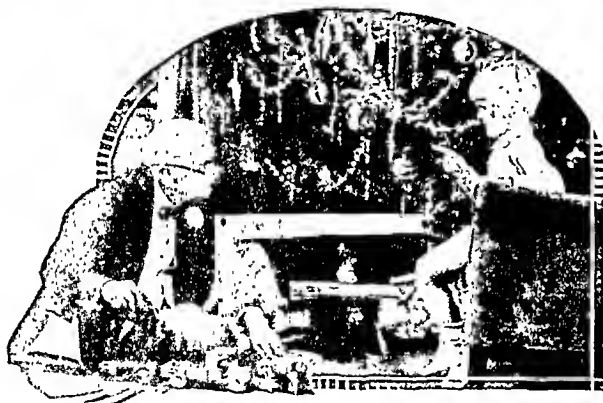
GORHAM, FRANK W. AND IVY, ANDREW CONWAY.

General Function of the Gall Bladder from the Evolutionary Standpoint. Field Mus. Nat. Hist. Publ. 417, Zool. Ser., 22(3):159-213, 1 fig., 1938.

A survey of the invertebrates for the occurrence of the gall bladder is presented. The gall bladder is a primitive organ peculiar to the Chordata. It serves the purpose of storing bile for digestion and the regulation of pressure in the biliary passages. It is uniformly present in amphibians

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and reptiles, in the monotremes and marsupials. It has been lost to some extent in those mammals which eat continuously or manifest continuous digestion, as in the herbivora, and is retained in those which tend to eat intermittently and possess a liver which forms small quantities of bile. Those mammalian spp. most closely related to the primitive stem retain the gall bladder; other orders vary. Some spp. such as the guinea pig, rabbit and cow possess a gall bladder, which does not concentrate well and hence stores very little of the total output of bile. In these spp. the gall

bladder can serve only as a pressure regulating mechanism. It appears that a sphincter of Oddi (sphincter choledocus) must have appeared in the evolutionary process concomitantly with a gall bladder since a sphincter is requisite for gall bladder filling and at the same time necessitates a pressure regulating device. Animals without a gall bladder possess no sphincter to prevent intestinal contents from regurgitation into the bile duct. Extensive tables and bibliography are appended.—K. K. J. (courtesy of Biological Abstracts).

GULZOW, M. UND AFENDULIS, TH. C.
Über die Stauungs gastritis. Tierexperimentelle Untersuchungen. Zeitschr. Ges. Exp. Med., 104(4): 465-488, 15 figs., 1938.

Acute congestion by ligation of the portal vein immediately above its junction with the pancreatic-duodenal vein, caused death of the experimental animals 2-5 hours after the operation (hemorrhage, edema, extreme distension of the gastric blood vessels). Chronic congestion was produced in 12 dogs after previous application of a gastric fistula by gradual narrowing of the lumen of the portal vein; the second part of the operation was carried out after 3 weeks in order to eliminate at this time the formation of a possible collateral circulation. The acidity of the gastric content showed a decrease, accompanied by a decrease in secretion and time of emptying, which was followed by an increase after 1-2 weeks. The gastrosopic picture, showed first venous congestion, followed by an erosive-hemorrhagic fibrinous hypertrophic gastritis. Ulcers did not develop regularly. Increase in histamin content of the portal and peripheral veins could be demonstrated by typical drop in the cat's blood pressure; the histamin formation was due to anoxemia, disturbed intestinal function, insufficient detoxifying ability of the damaged liver. Assumedly, histamin and related substances were of importance for the etiology of the gastritis which was of hematogenic toxic origin.—M. S. (courtesy of Biological Abstracts).

BING, J. AND BROAGER, B.

Investigations of the Effects of Nicotinic Acid on Two Patients with Idiopathic Steatorrhea (Sprue). Acta Med. Scand., 97 (5/6):561-577, 3 figs., 1938.

The amount and water content of the faeces were altered, but with no increased absorption of dry substance, lipid, nitrogen, Ca or ascorbic acid. On suspending treatment the diarrhea returned. None of the many other sprue symptoms was so distinctly modified as the diarrhea.—M. G. C. I.—(courtesy of Biological Abstracts).

IRWIN, MARGARET HOUSE, WEBER, JANET, STEENBOCK, H. AND GODFREY, T. M.

The Influence of Hydrogenation and Oxidation of Fats Upon the Rate of Absorption. Am. J. Physiol., 124(3):800-803, 1938.

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The earliest techniques for determination of vitamin A were similar in that they all first provided for depletion of the body stores of vitamin A of the rat by restriction of the animals to basal rations free from or quite deficient in the vitamin. In the "rat growth" method, the vitamin A activity of the material under assay was estimated by feeding graded dosages to animals depleted of the vitamin (as gauged by cessation of growth) and recording the ensuing growth response (2). In the "curative technique," the incidence of xerophthalmia served as the criterion of vitamin A depletion (3), and vitamin A activity was estimated by determining the dosage of the test material necessary to establish cure of xerophthalmia.

Techniques were also gradually developed which in some instances embodied features of both the growth and curative methods. Still another technique based on the continuous appearance of cornified epithelial cells in vaginal smears—a further characteristic of vitamin A deficiency in female rats—was evolved (4). Further research showed that colorimetric and spectrographic methods may be adapted to the estimation of vitamin A activities of specific materials (5).

Of all methods for estimation of vitamin A in foods, the rat growth technique appears to be favored today (6). Gradual improvements and refinements—as well as recognition of the existence of provitamins A—have led to development of the growth method now included in the U. S. Pharmacopeia XI. This method requires that young rats weighing 10 to 50 grams (at an age not exceeding 28 days when placed on a vitamin A deficient ration) shall manifest symptoms characteristic of vitamin A deficiency within a period of 25 to 45 days. Rats properly depleted of vitamin A reserve are assembled in negative control groups receiving no supplement, reference groups receiving graded doses of the standard reference material, and assay groups receiving graded doses of the assay material. During the ensuing period of not less than 28 days, the test animals are fed daily doses of the proper supplements. The body weights of the animals are recorded at frequent intervals during and at the end of the assay period. From the average gains in body weight of rats in the assay and reference groups, dosages of assay and reference materials, and the vitamin A activity of the standard of reference, the vitamin A activity of the assay material is calculated.

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- (1) 1913 J Biol Chem 16 473 and 255
- (2) 1918 J Biol Chem 66 1
- (3) 1931 J Dairy Sci 14 779
- (4) 1927 J Biol Chem 73 153
- (5) 1938 J Am Med Assoc 111 715

- (6) 1936 The Pharmacopeia of the United States, Eleventh Decennial Revision page 478
- (7) 1929 Ind Eng Chem 21 347
- 1936 J Am Diet Assoc 12 231
- 1936 Mass Agr Expt Sta Bull No 339
- 1938 Nutrition Abstracts and Reviews 8 281

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melting points exceeded body temperature the rate of absorption was progressively reduced. Hydrogenated cottonseed oil oxidized by aeration but of practically constant melting point was absorbed at a decreasing rate with increasing peroxide number.—H. S. (courtesy of Biological Abstracts).

BAGGENSTOSS, ARCHIE H.

Major Duodenal Papilla: Variations of Pathologic Interest and Lesions of the Mucosa. Arch. Path., 26(4):853-868, 3 figs., 1938.

An investigation at the Mayo Clinic of 100 major duodenal papillae of man disclosed the following findings

of pathologic interest—a junction of bile duct and pancreatic duct occurred in 33 of 55 specimens examined and in only 6 of these specimens was the ampulla 5 mm. or more in length; marked narrowing of the bile and pancreatic ducts occurred as they pierced the duodenal wall; polyps of the papilla were found in 4 of the 100 specimens. Lesions of the major duodenal papilla which have been observed in routine postmortem examinations at the clinic, up to October 1, 1936, include two cases of ulceration, 2 cases of edema, 25 cases of polyp and 28 cases of carcinoma (0.21 per cent). In 15 cases of carcinoma of the major papilla, there was no evi-

dence of metastasis. 3 cases of carcinoma of the minor papilla were also observed.—A. H. B. (courtesy of Biological Abstracts).

CAMERON, G. R. AND DE SARAM, G. S. W.

The Effect of Liver Damage on the Action of Some Barbiturates. J. Path. and Bact., 48(1):49-54, 1939.

Rats with acute liver damage are more susceptible than normal animals to the quickly acting barbiturates, pentobarbital Na and evipan Nn. This effect quickly passes off when liver regeneration sets in. With progressive, liver damage, as in the pre-cirrhotic stage of CCl₄ cirrhosis, the action of pentobarbital Na is greatly enhanced long before serious structural damage has appeared in the liver. It is suggested that impairment in detoxifying function precedes the development of cirrhosis.—Authors (courtesy of Biological Abstracts).

GOODPASTURE, W. CARTER, VERMEULEN, DONOVAN, PAUL B. AND DRAGSTEDT, LESTER R.

The Bromsulphalein Liver Function Test as a Method of Assay of Lipoeic. Am. J. Physiol., 124(3):642-646, 1938.

Impaired liver function as evidenced by abnormal retention of bromsulphalein has been found in the large majority of insulin-treated depancreatized dogs that develop fatty infiltration in the liver. The disturbance in liver function was found to be roughly proportionate to the amount of fatty infiltration and was promptly corrected by lipoeic administration. Accordingly, the bromsulphalein test was suggested as an additional criterion of lipoeic deficiency in depancreatized dogs and possibly also in diabetes mellitus.—Authors (courtesy of Biological Abstracts).

BELL, E. T.

A Clinical and Pathological Study of Subacute and Chronic Glomerulonephritis, Including Lipoid Nephrosis. Am. P. Path., XIV, 6, p. 691, Nov., 1938.

This report represents a study of 181 cases of subacute and chronic glomerulonephritis which have been classified in accordance with certain clinical and pathological features into the following groups:

- I. Subacute glomerulonephritis.
- II. Chronic glomerulonephritis in which death was due to an intercurrent disease.
- III. Advanced chronic glomerulonephritis of azotemic type.
 - A. With history of acute glomerulonephritis.
 - B. No history of acute nephritis,



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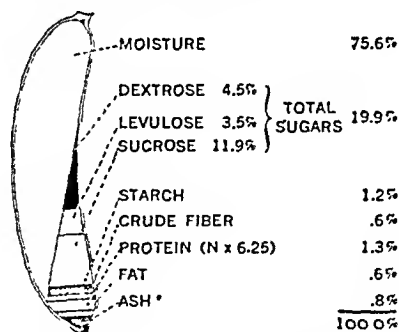
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the kidneys weighing 250 gm. or more.

C. No history of acute nephritis, the kidneys weighing less than 250 gms.

IV. Chronic glomerulonephritis of the hydropic type.

A. With glomerular structure of chronic proliferative glomerulonephritis.

B. With a glomerular structure largely membranous but partly of proliferative type.

C. With a normal glomerular structure or a strictly membranous glomerulitis.

Subacute glomerulonephritis. This group bleeds from the acute into the chronic type. Cases terminating in uremia after a few months are called subacute. The kidneys are normal in size or enlarged. There is severe uniform obstruction of all the glomeruli, but there are no hyaline glomeruli. There is moderate uniform atrophy of the tubules; there is very little atrophy in the acute type. In the chronic type there are patches of extremely atrophic tubules associated with hyaline glomeruli.

The blood pressure is usually high. Retinal edema and hemorrhages are frequent. Abundant albumin and

casts are found in the urine, but hematuria is infrequent. Edema is usually marked and the plasma proteins low. Death was due to uremia in all of the author's cases.

The pathogenesis of the glomerular lesion in chronic glomerulonephritis may be traced much as follows. The normal glomerular lobule is composed of capillaries with a distinct basement membrane in both inner and outer walls. In acute glomerulitis there is an increase of endothelial cells and the central basement membranes of the capillaries are split into numerous irregular fragments—intracapillary fibres. In severe glomerulitis the capillaries are completely obstructed but in less severe lesions from which the chronic forms probably develop, the capillaries are not closed completely. As the inflammation subsides the blood forces the intracapillary fibres to the center of the lobule where they become fused to form a central hyaline mass. If the capillaries are completely closed during the acute attack the glomerulus becomes hyaline. The chief difference between the early and mild lesion and the advanced azotemic type is the difference in the number of hyalinized glomeruli. The advance from the early to the late stage of chronic glomerulonephritis is probably due to repeated acute attacks which obstruct more and more of the glomerular circulation.

The total course of the disease in advanced glomerulonephritis of the azotemic type varied in the author's series between 18 months and 26 years; the average being 10 years. The acute attack is usually followed by a latent period when the patient considers himself well. The acute attack may have been severe or so mild as to have been overlooked. There may be repeated acute exacerbations during which all symptoms become more intense. The blood pressure is usually somewhat elevated, 150 mm. hg., to become higher toward the end of the disease. In a few cases going on to death no elevation of blood pressure has been noted; and in others very high pressures, 275 mm. hg. have been recorded. The average weight of the heart was 456 gm. It varied from 200 to 700 gms. The hypertrophy was of the left ventricle. The renal function remained fairly stationary, 25 to 50 mg. per cent blood urea nitrogen—until the terminal stages when it failed rapidly. When the urea nitrogen reached a level of 100 mg. per cent the patient lived usually but a few weeks. The phenolsulphonephthalein test ran parallel with the urea nitrogen. Hypochromic anemia was usually present as was also retinal exudates and hemorrhages. Edema varied

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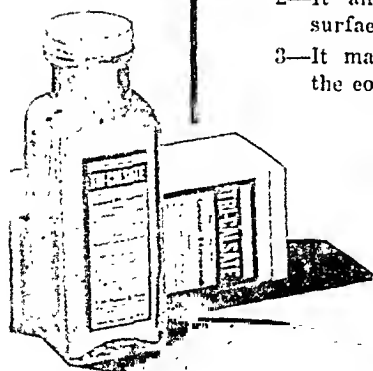
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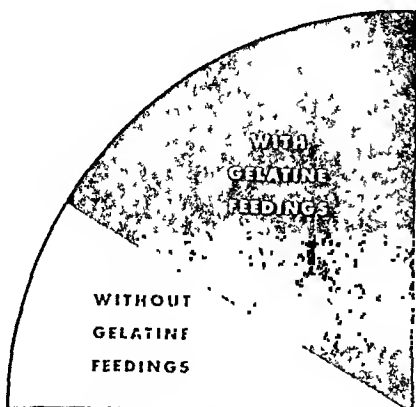
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'Proceedings of the Society for Experimental Biology and Medicine', 40 157, 1939.

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greatly in different cases, often present in the acute beginning to disappear later, but sometimes only present at the end. It depends probably more on the level of the plasma proteins than other factors. There was no apparent relation between edema and the size of the kidney in this group. There was also no definite relation between the size of the kidney and other clinical features, as the heart size and the blood pressure. As a rule a continued edema usually accompanied a large kidney.

The variations in the size of the kidneys in the terminal stages of chronic glomerulonephritis were re-

lated to the structural changes that had taken place.

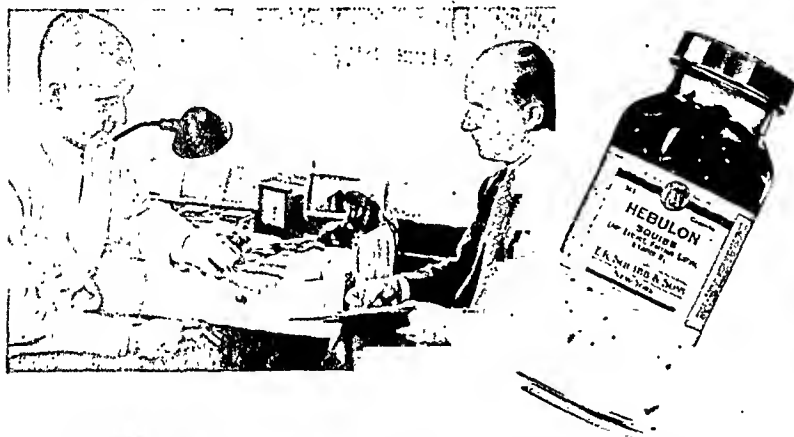
In acute glomerulitis the capillaries show lesions ranging from no obstruction at all to complete obliteration. When the glomeruli have suffered no or little narrowing, glomerular filtration continues and the tubules are unaffected, but when the capillaries are closed the glomerulus becomes hyaline and the tubules disappear entirely or become epithelial cords. The degree of kidney atrophy corresponds to the degree of the glomerular involvement. When many glomeruli are partially damaged and the corresponding tubules are only

partially affected renal insufficiency may result without the kidney having undergone any contraction.

The most common form of chronic glomerulonephritis is the small contracted kidney of usually less than 200 gm. weight. The cortex is thin and the majority of the glomeruli are hyaline and their tubules have almost disappeared. Eighty to 90 per cent of the visible glomeruli are hyaline and many have probably been absorbed by phagocytes. A terminal acute glomerulonephritis is at times found superimposed on a chronic form, as these glomeruli then show fresh epithelial crescents and other acute changes. When arteriosclerosis is associated with the chronic lesion a very high blood pressure has previously existed. In the group of chronic glomerulonephritis in which the kidney is of normal or even of greater than normal weight, the number of hyaline glomeruli present is less than one-half of the total number seen, and may be as few as 10 or 20 per cent. The most frequent nephron in these large kidneys is a damaged glomerulus with moderate atrophy of its tubule. The renal cortex then is not much shrunken. Arteriosclerosis may likewise be associated at times with this form of nephritis. As damaged glomeruli and tubules have a reduced functional capacity uremia may develop, as it does in the subacute type, before a large number of glomeruli have become hyaline. It is probable that repeated infections are responsible for the progressive failure of renal function in chronic nephritis.

In chronic glomerulonephritis of the hypoplastic type edema was a prominent feature throughout the greater course of the disease. Both edema and albuminuria increased, however, at times in the form of acute exacerbations. The author describes three subgroups of this form of nephritis, all lipid nephrosis in a clinical sense, but differentiated one from the other by histological differences in the structure of the glomeruli. The first subgroup histologically was a chronic proliferative glomerulonephritis in which death occurred from edema early in the disease. The kidneys were large, yellowish tinged on section and smooth surfaced. All glomeruli were enlarged and uniformly involved. The lobules showed central masses of hyaline formed by thickening and fusion of the centrally placed capillary basement membranes. There was no diffuse thickening of the capillary basement membranes of the glomeruli, which characterizes most cases of lipid nephrosis. Thus chronic proliferative glomerulonephritis may reproduce the clinical syndrome called "lipid nephrosis."

The second subgroup presented the clinical picture of lipid nephrosis,



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but added to it was some hypertension, some azotemia and one patient died of uremia. The histological glomerular picture was partly of the membranous and partly of the proliferative type. They were mainly large with many permeable capillaries; there were only a few hyaline glomeruli present. The membranous type predominated over the proliferative type.

In the third subgroup with the clinical diagnosis of lipoid nephrosis the glomeruli showed no evidence of proliferative glomerulitis. In 6 of the cases there was no visible change in the glomeruli whatsoever, although

there was a little elevation of blood pressure, but not progressive, and a little decrease in renal function. Those cases with elevation of blood pressure usually showed thickened basement membranes in the glomeruli. Aside from this there was no difference clinically in the cases without any change in the basement membranes from those with patchy thickening or with marked thickening. The plasma proteins were markedly reduced; and cardiac failure played no role in the edema formation. Four deaths occurred from uremia and 17 out of 25 from infectious processes. In a tabulation of

53 cases from the literature 42 died from peritonitis. Exacerbations and remissions occurred during the course of the disease. The former often followed an upper respiratory infection. Histologically there is no primary tubular atrophy. Atrophy of the tubules occurs only when the capillaries of their associated glomeruli are obstructed. Lipoid nephrosis, therefore, is not a primary tubular disease. In young children in which the capillary basement membranes show little or no structural changes it must be believed that they have nevertheless suffered damage because all gradations of membrane changes are found as the patients become older. The thickening of the membranes in some way appear to be related to age. The convoluted tubules often contain droplets of lipoid, but they never show primary degeneration or necrosis. Atrophy of the tubules in lipoid nephrosis, as in the other forms, follows closure of the glomerular capillaries. It is due to primary glomerular disease and not to primary tubular degeneration as Th. Fahr maintained. Uremia may develop in the case in which there is partial closure of the capillaries causing a diffuse tubular atrophy of moderate degree, as well as in the case with shrunken kidneys from hyalinization and absorption of many glomeruli.

In conclusion the author discusses the historic development of the subject of nephritis, laying special stress upon the theories of Volhard and Fahr. However, he maintains with complete logic that the various forms of glomerulonephritis, among which lipoid nephrosis is included, depend upon the extent and character of their glomerular lesions. If the initial acute attack is severe and causes widespread capillary obstruction, renal insufficiency soon develops. If death occurs in a few months from uremia it is called acute; if in 4 months to a year it is called subacute. When the initial glomerular injury is less severe so that the majority of the capillaries remain permeable a chronic nephritis develops. Complete anatomic recovery may occur after mild acute injury. The initial glomerular lesion consists of an increase of endothelial cells and splitting and fragmentation of the central capillary basement membranes in the interior of the lobules. If the capillaries become completely occluded the glomerulus becomes hyaline; if partially occluded a peripheral circulation develops in the lobule and the hyaline fibers, derivatives from the central membranes, become fused into a hyaline mass at the center of the lobule. Azotemic glomer-

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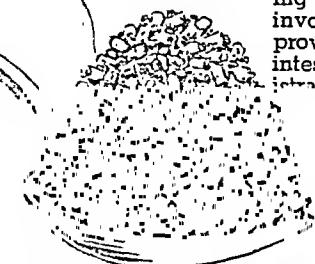
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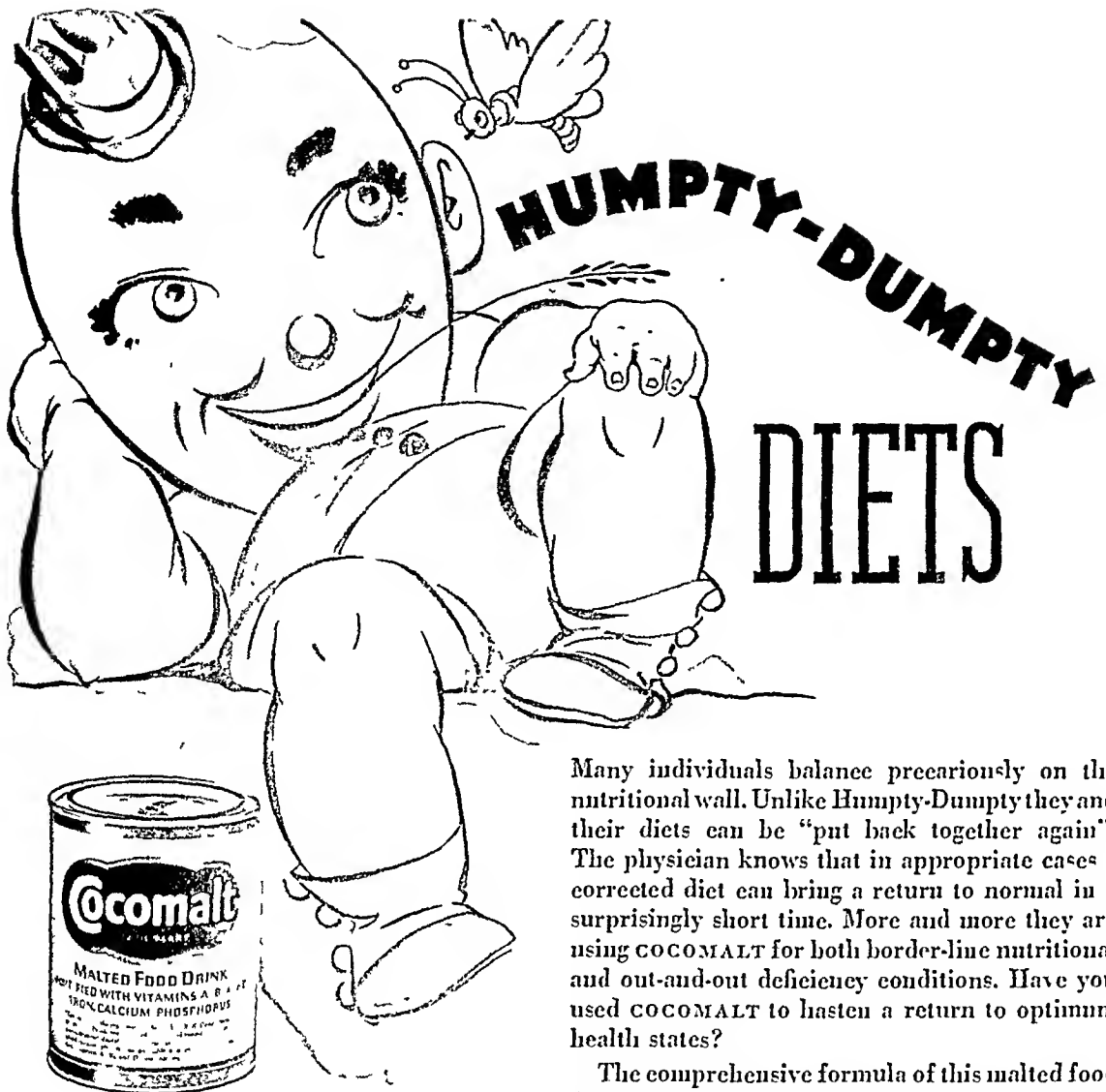
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ulonephritis is characterized by widespread obstruction of the glomerular capillaries. In hydropic glomerulonephritis the capillary walls are injured but the lumens remain open. This lesion is characteristic of membranous glomerulitis. The hydropic form rarely occurs in proliferative glomerulitis. It is not known whether the same etiologic factors produce the two forms or not; it is known only that proliferative glomerulitis blocks the capillaries whereas the membranous type permits an escape of the plasma proteins. This permeability of the capillaries causes edema, the out-

standing feature of the disease. Hypertension does not develop until the thickened membranes have produced a definite narrowing of the capillary lumens. In brief, therefore, azotemic nephritis is due to capillary obstruction and hydropic nephritis results from increased permeability of the capillaries to proteins. Azotemia develops regularly in proliferative glomerulitis but infrequently in the hydropic form. Hydropic glomerulonephritis is usually due to membranous glomerulitis, but occasionally is seen with the proliferative form.

N. W. Jones, Portland, Oregon.

BOLDYREFF, W. N.

The Pavlov Gastric Pouch. Some Historical Data. From the Pavlov Physiological Institute of the Battle Creek Sanitarium, Battle Creek, Michigan.

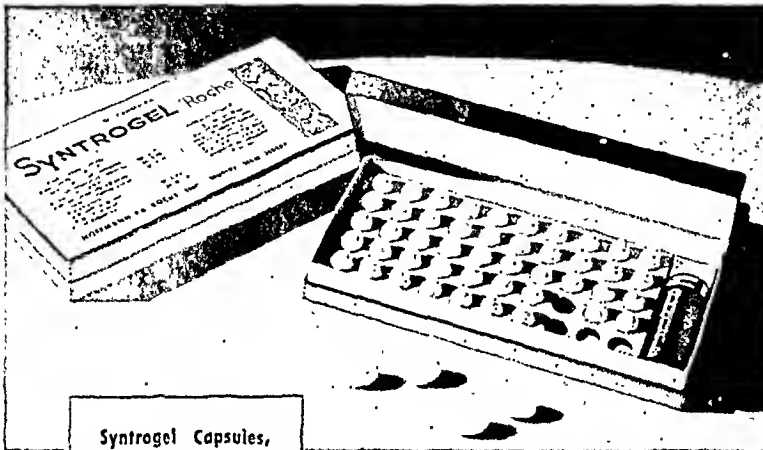
This article is prompted by the recent publication of Jemerin and Hollander (1) who properly pointed out that in some cases Pavlov pouches, as made, are really Heidenhain pouches in that they have little or no vagal nerve supply. This is due to the way in which the various branches of the vagus nerves spread over the external surface of the stomach. Jemerin and Hollander's work is important because it emphasizes the necessity of preserving an adequate nerve supply to the isolated bit of stomach if it is to be looked on as a Pavlov pouch.

I thought it might be of interest to record here some of the early historical facts about these pouches which I happen to know because I spent a number of years in Pavlov's Institute during the time in which he was so interested in the physiology of gastric secretion.

The real pioneer in the recognition and utilization of a new method for the study of gastric physiology was Beaumont (3). The gastric fistula method used by him was employed in dogs by Bassoff (Moscow, 1840) (4) and Blondlot (Paris, 1842) (5). Thiry in 1864 isolated a loop of intestine for study. This appears to have been the first effort to isolate a portion of an organ and leave it in situ for study. Klemensiewicz (6) in 1875 prepared a pouch of the pyloric portion of the stomach. This work was followed in 1878 by the production of an isolated pouch of the fundic portion of the stomach by R. Heidenhain (2). His operation is simple and easily performed. Pavlov (7), recognizing disadvantages due to the absence of a vagal innervation to the Heidenhain pouch, in 1894 introduced, with the help of P. P. Higin (8) or Khigine, his well-known method for making a pouch with most of the vagal nerve supply intact (7). In 1905 Cade and Latarjet (9) studied gastric secretion secured from a pouch accidentally made in a man.

Many persons who attempted to make Pavlov pouches failed, and some doubtless injured the vagal branches to such an extent that the pouch later did not respond to psychic stimuli.

Jemerin and Hollander state that nowhere in the work of Pavlov and Khigine did they indicate that they had carried out actual dissection to demonstrate the course of the vagi. Instead Khigine in his original thesis referred to Ellenberger and Baum (16) whose description and illustration he utilized. Jemerin and Hol-



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* For a full summary of these experiments as reported in September issue of *The Journal-Lancet*, write Libby, McNeill & Libby Research Laboratories, Dept. AD-12, Chicago.

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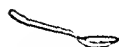
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REPRINTS of the Editorial "Aids to Normal Bowel Function," "Amer. J. Dig. Dis.," March, 1939, J. A. Bergen, M.D., will be supplied on request.

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lander also stated that the Pavlov pouch technique was based upon the erroneous anatomical concept that only the ventral trunk runs along the lesser curvature, whereas the dorsal trunk courses along the greater curvature.

It must be remembered that Pavlov was highly conversant with the anatomy and physiology of the vagus nerve and its branches. With Khigine, Pavlov devoted three years to the anatomical and surgical studies which led up to the production of his pouch.

During the ten years in which I prepared demonstrations for Pavlov he was always much interested in the vagus nerves, and he always insisted on studying them whenever some dissection brought them into view. Regardless of what is shown in the diagrams published in his various papers, Pavlov always made the incision in such a way that one-tenth or never more than one-eighth of the incision went perpendicular to the branches of vagus nerves as shown in the dissections of Jemerin and Hollander (1). The incision in the mucosa was made so as to preserve the remainder of the nerve supply. Furthermore, and this is the important point, about a month after performing the operation, Pavlov would always test the animal for psychic secretion, and discard it if the pouch did not respond.

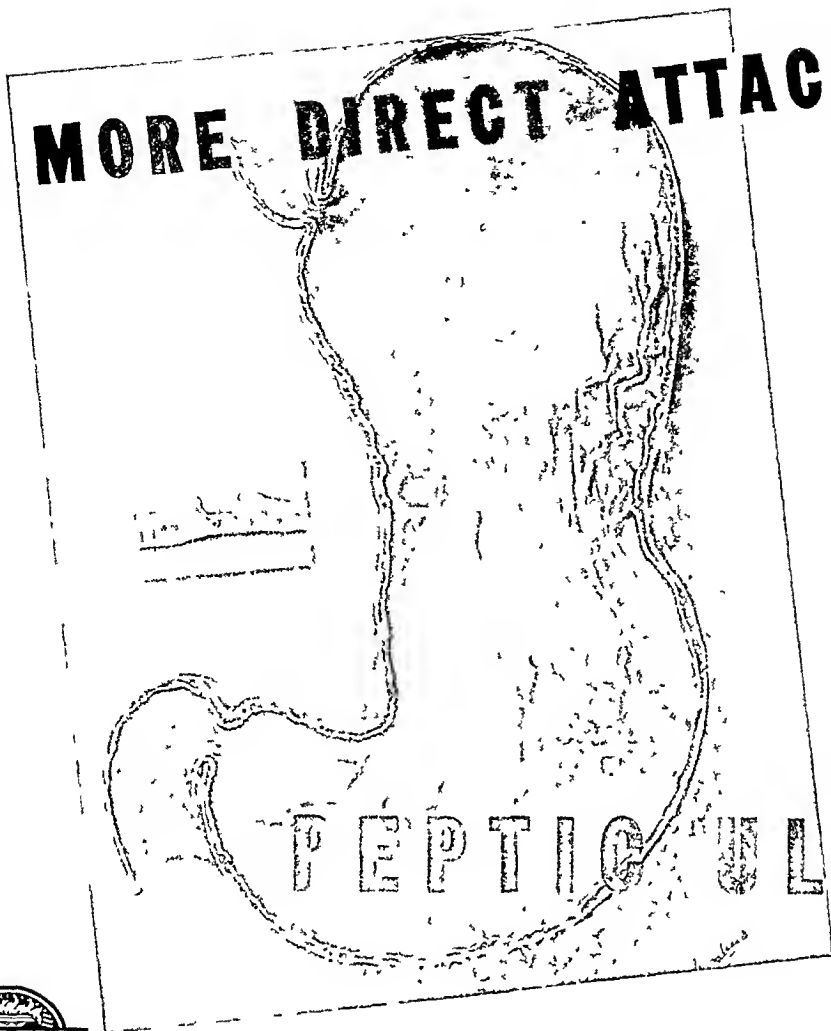
Anyone who will study Pavlov's published protocols will note that he usually made small pouches so as to be certain that the isthmus or the portion of serosa and muscularis and nerves cut was small; this is indicated by the relatively small amounts of secretion which he usually obtained and recorded. To obviate this difficulty, I simplified Pavlov's technique and made larger pouches. This was done by making an incision in the ventral wall of the stomach and completing the incision of the mucosa through the opening. This sectioned some vagal fibers in the ventral wall, but none elsewhere (10-18). Such pouches not only manifested a psychic secretion, but they secreted relatively large quantities of juice.

It should be emphasized that the crucial test for determining if one has made a true Pavlov pouch should not be an anatomic but a physiologic one, namely, one should test to see if the pouch will secrete in response to psychic influences. The observations of Hollander and Jemerin will serve to emphasize the importance of preserving the maximum amount of nerve supply to the pouch.

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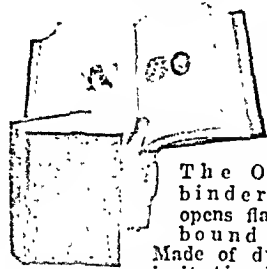


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MALKIN, J. I. AND MARKOW, H.

Analysis of the Comparative Results of Skin Testing with Cooked and Uncooked Foods. J. Allergy, 10:337, 1939.

A large series of allergic patients were skin tested with extracts of raw foods and extracts of the corresponding cooked foods in an effort to determine to what extent heating denatures foods. Seven hundred and eleven pairs of intradermal tests were done and in 652 (91%) instances, the reactions with the two extracts were considered equal. In 3.9% of the tests the raw extract yielded a positive test and the cooked one a negative one, while in 4.3% the cooked extract was positive while the raw one was negative. The authors believe that the differences between reactions with raw and cooked extracts is not sufficient to warrant any change in the present methods of preparation of allergenic extracts.

EHRENFELD, I., BROWN, A. AND STURTEVANT, M.

Allergy in the Pathogenesis of Peptic Ulcer. J. Allergy, 10:342, 1939.

A series of 75 patients with proven peptic ulcers were subjected to routine allergic studies. No relationship between ulcer and atopy could be es-

tablished. A group of 72 allergic subjects were then investigated for the incidence of peptic ulcer. A few patients among this group gave histories of gastro-intestinal symptoms which consisted chiefly of spasm of the stomach and duodenum. The incidence of urticaria and angioneurotic edema was higher among allergy patients having gastro-intestinal complaints. The authors conclude that allergy is rarely associated with peptic ulcer.

GERSHON-COHEN, S., SHAY, HARRY AND FELS, S. S.

Experimental Studies on Gastric Physiology in Man. IV. The Influence of Osmotic Pressure Changes of Salt and Sugar Solutions on Pyloric Action and Gastric Emptying in the Normal and Operated Stomach. Am. J. Roent. and Radium Therap., 40 (8):335-343, 6 figs., 1938.

The influence of duodenal osmotic change on gastric motility and on the action of the pylorus was studied roentgenographically. The standard test meal consisted of 2 oz. of barium sulfate in tap water, at or near body temperature, to which salt and sugar solas. of various osmotic tensions were added. For both normal and operated stomachs, the greater the hypertonicity of the test meal, the slower was gastric emptying.—E. H. Quimby (Courtesy of Biol. Abst.).

HEINANEN, N.

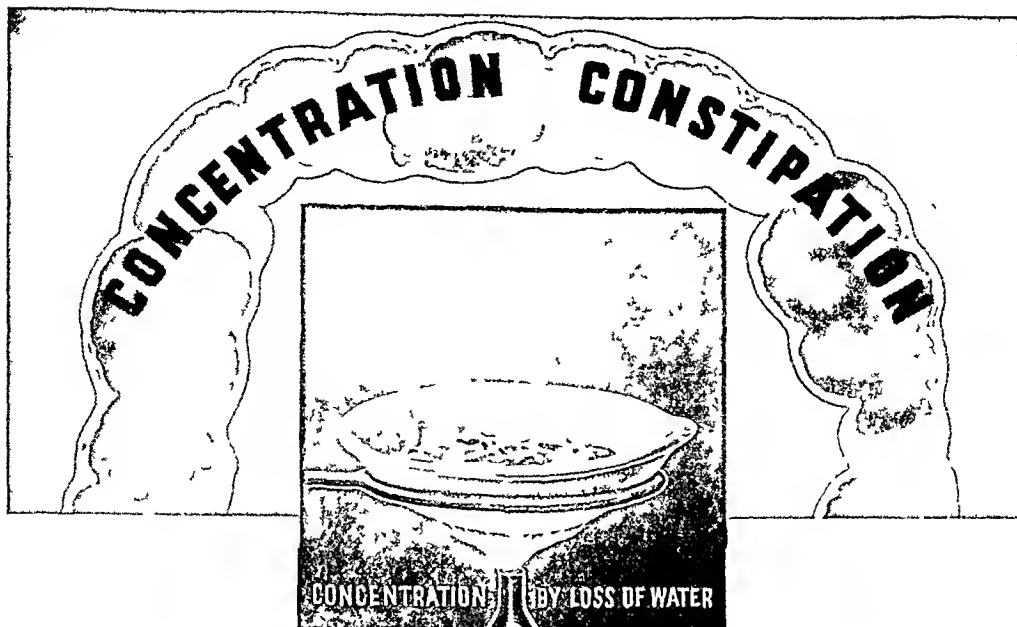
Welche Resultate gibt die interne. Behandlung der Ulkuskrankheit? Acta Med. Scand., Suppl. 89:327-331, 1938.

The late results do not correspond with those obtained under hospital treatment. This may be due to the type of patient (artisans) who cannot follow their dietetic treatments adequately.—J. F. Wilkinson (Courtesy of Biol. Abst.).

MACLACHLAN, P. L. AND HODGE, HAROLD CARPENTER.

The Influence of Cocaine Feeding on the Liver Lipids of the White Mouse. J. Biol. Chem., 127(3): 721-726, 1939.

Albino mice were given graded and increasing doses of cocaine hydrochloride per os. The livers were taken after 60 days and the lipids studied chemically and histologically. A vacuolar degeneration was observed in every case and an extensive fatty infiltration in nearly half the cases. Neutral fat and cholesterol increased greatly in the latter cases, the neutral fat more than the cholesterol. In contrast, the phospholipids showed a striking constancy, emphasizing the importance of these substances as true cellular constituents. — H. C. Hodge (Courtesy of Biol. Abst.).



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*Welch, P. B., and Kauders, F. H. The Physiologic Approach to the Correction of Constipation, South M. J. 31 709 (July) 1935

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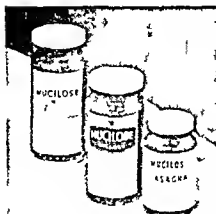
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CONNOTATIONS

H. J. SIMS

Denver, Colorado

Grassers reported 188 cases of obturator hernia found in the literature between 1720 and 1890. Meyer states that 51 of these cases were reported prior to 1875. Englisch's textbook which appeared in 1891 stated that Hahn reported two cases in which the bladder was present in the hernia. Kronlein in 1890 described a strangulated obturator hernia which contained the uterus, ovary, tube, and a loop of small intestine. Rogner-Gusenthall observed a strangulated tube and ovary both of which were gangrenous. Chiene in 1870 recognized a portion of the ileum and the outer two-thirds of the left tube and the whole of the left ovary in a hernial sac.

According to Mueller, Ambrose Pnre in 1558 drained an abscess from the knee and unexpectedly found a loose cartilage. In 1691, Pechlin, a Swedish surgeon described the symptoms accompanying this condition. Monroe in 1726, Simpson in 1736, and Morgagni reported similar cases. Benjamin Bell in 1787 advised amputation of the leg. He remarked: "The remedy is severe but is less painful and hazardous." Laennec in 1813 described the formation of these bodies. Larry in 1860 collected 170 cases submitted to surgery; 117 were successful, 33 died and 20 were failures. Recklinghausen reported the presence of loose bodies in case of arthritis deformans. Berry in 1894 removed 1047 free bodies from a joint which four years earlier had 50 similar bodies removed. The concretions surrounded a nucleus of cartilage and varied in size from a fine bead to a pea.

The older text-books of surgery, written by P. Franco as late as 1561 made no mention of lumbar hernia. In 1672, Pnul Barbette said "Experience has taught me that the peritoneum may rupture in its posterior aspect thus forming a hernia." Dolle is often credited as describing a lumbar hernia; however, there is nothing in his Latin writings to indicate his knowledge of this anomaly. Budgeon in 1728 described such a hernia, but there is some doubt as to whether his patient actually suffered from a lumbar hernia, for he describes his patient as presenting a congenital tumor in the region of the kidney, which ruptured at the age of 17 years. It has been suggested that the tumor was perhaps a spina bifida or hydronephrosis.

Gargangeot observed a strangulated lumbar hernia, and Ravaton in 1750 published a report of successful operation of a strangulated hernia. Petit is often given credit for describing the triangle through which lumbar hernias protrude. The writings of Petit makes no reference to anatomical data on this subject.

MELLANBY, J. AND SUFFOLK, S. F.

A Quantitative Investigation Into the Enterohepatic Circulation of Bile Salts in the Cat. Proc. Roy. Soc. (London) Ser. B., 126(844):287-302, 1938.

In a fasting cat about 95% of the total bile salt is contained in the gall bladder bile. The hepatic bile, continuously secreted by the liver, contains only traces of bile salt. In the fed cat the vol. and bile salt content of the hepatic bile shows a large increase while the gall bladder contains only a small quantity of relatively dilute bile. The removal of the small intestine causes an immediate fall in the cholic acid content of the hepatic bile to that found in the fasting cat. Bile salts are absorbed more rapidly from the ileum than from the duodenum and jejunum. A small amount of absorption occurs in the large intestine but the absorption of water takes place much more rapidly than that of bile salt. Consequently, the original conc. of bile salt may be increased fivefold in the unabsorbed bile. Bile salts injected into the blood are rapidly excreted in the hepatic bile. They are non-threshold substances in respect of the biliary apparatus. Bile salts

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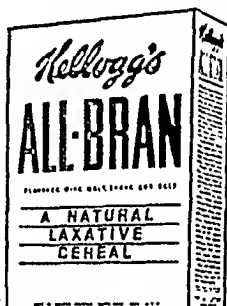
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SECKEL, H. P. C.

The Influence of Various Physiological Substances on the Glycogenolysis of Surviving Rat Liver. Methods; Influence of the Bile Salts. Endocrinology, 23(6):751-759, 2 figs., 1938.

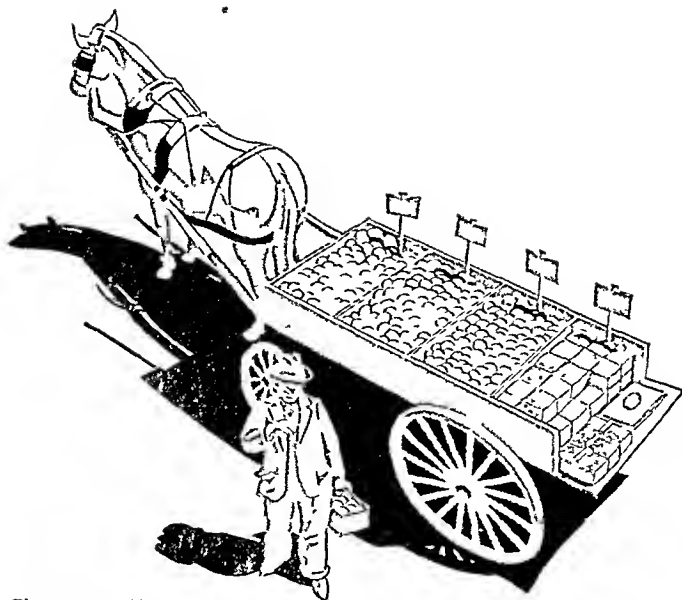
Lesser's method of estimating the "dynamic efficiency" of frog liver lobes was modified for warm blooded animals by determining the 60 minute decrease in glycogen of rat liver slices surviving in a buffer solution at 37° C. The effect on this system of various concentrations of 2 bile-salt preparations containing different properties of Na glycocholate and taurocholate was studied in 62 experiments. By expressing the "bile-salt glycogenolysis" in terms of + and — deviations from "bile-salt-free glycogenolysis" a bi-

phasic curve in bile-salt glycogenolysis was obtained. The positive phase of this curve occurred at low concentrations, the negative phase at high concentrations. The physiological action of the surface-active bile salts on the intracellular fixation of the glycogenase to the protein boundary structures of the liver cells is discussed. The relationships of the findings to Forssgren's daily cycle of the liver function, artificial and pathological obstructive jaundice, and von Gierke's glycogen storage disease is considered.—D. Permer (Courtesy of Biol. Abst.).

HOREJSI, J. MECL, A. AND SPISAROVA, J.

The Metabolism of Aminoacids and Liver Functions. Acta Med. Scand., 96(2/4):217-230, 4 figs., 1938.

Urea concentration and amino-N are of no value in hepatic function determinations, while the ammonia excretion can only be used with caution. The glycine tolerance is of value. Insulin has a similar but less effect on amino-N to that on blood sugar. Urea excretion is valuable in estimating hepatic function, a rising excretion after glycine and a falling nitrogen quotient are a favorable sign. There is reasonable agreement with results obtained by other tests for hepatic function.—J. F. W. (courtesy of Biological Abstracts).



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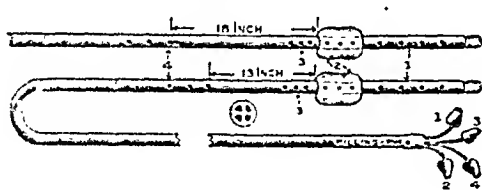
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VELICK, SIDNEY F., WHITE, JULIUS AND LEWIS, HOWARD B.

The Synthesis of Dicholyleystine and Cholyleystic Acid. J. Biol. Chem., 127(2):477-481, 1939.

The peptide, dicholyleystine, has been synthesized and its oxidation to cholyleystic acid described. The compounds are of interest in view of the suggestion that the conjugation of cholie acid with cystine may occur in the biological synthesis of taurocholic acid.—J. White (Courtesy of Biol. Abst.).

CONNOTATIONS

H. J. SIMS

Denver, Colorado

DeBeule recognized and named the "en w" type of incarcerated hernia. Lauenstein in 1894 first described this type of hernia. Maydl in 1895 described 2 cases of strangulated hernia; in the first case, the distal end of the hernia remained in the abdomen, and the sac continued the appendix. In the second case, the Fallopian tube was involved in the same manner as the appendix. In both instances, the distal ends of the organs were gangrenous, and that part contained within the sac showed only mild circulatory disturbances. Maydl used the term "retrograde incarceration" to describe the condition. Schmidt in 1880 described such a formation in a strangulated umbilical hernia. Friedman in 1913 reviewed the cases reported in the literature.

Hey in 1814 used the name, infantile hernia, to describe an encysted hernia. It has been suggested that he used the term because his description was drawn from an infant with such a hernia. Cooper in 1827 described this variety of hernia and is usually given credit for its recognition.

Erythromelalgia was first described by Wier Mitchell in 1872. In 1878 he used the term erythromelalgia, signifying a red painful limb.

The production of an artificial communication between the venous canal and portal vein for the relief of portal cirrhosis was first described by Eck, a Russian surgeon, in 1877. His work was confined to animals. Vidal of France, carried out this procedure on man. The patient lived four months and died of cardiac disease. Rosenstein performed the second operation with temporary relief.

Primary malignant disease of the appendix was recognized by Merling in 1838. The incidence occurred in a young girl dying from general peritonitis. Kalaszek in 1875 and Rokitsky in 1867, each reported a case. In the absence of a microscopic examination and an inadequate description, the diagnosis is problematical. Wenzel-Gruber in 1875 observed a cyst of the appendix. Lafforgue in 1893 found only 17 tumors of the appendix in the literature. Among these there were 1 lipoma, 1 myoma, 2 lymphadenomas and 2 hydatid cysts. Murphy recorded 2 cases, and Oviatt and Carson a single case of myoma of the appendix. Kelly in 1905 reported a fibroid tumor of the appendix.

BRENNEMAN, W. R.

Variations in the Reaction of Chicks to Different Methods of Administering Androgens. Endocrinology, 24(1):55-62, 1939.

Using White Leghorn cockerels, it was found that the relative effectiveness of oreton and oreton-B, as measured by comb growth, was the same whether injected subcut. or intraperit. Both were more efficient administered subcut., but comb growth was always greater with oreton-B. Androstenedione and dehydroandrosterone were less effective than oreton or oreton-B. Androstenedione plus oreton-B was more effective than oreton plus oreton-B. Body weight was essentially the same in both control and injected chicks until after cessation of injections; then controls became progressively heavier. Baby cockerels given oreton plus oreton-B for the first 5 days after hatching grew on the 7th day. Birds given oreton-B alone but in

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an amount equal to combined dosage of oreton plus oreton-B crowded on the 5th day of age.—D. Permar (Courtesy of Biol. Abst.).

RENTZ, Ed.

Über den Einfluss der Vagusreizung auf die Bewegungen des Dickdarms. Arch. Exp. Path. u. Pharmacol., 191(2):172-182, 12 figs., 1938.

Studies of the guinea pig and rabbit colon in situ with recording by Straub's technique showed that the proximal colon responded in essentially the same manner as the small intestine to electrical vagus stimulation. Results were less certain with the distal colon. Often, after a latent period of a few minutes, there was a general transitory augmentation of function. Disturbed rhythm in the fatigued colon was made normal, or stopped peristalsis was overcome. A reaction like that of the small intestine to electrical vagus stimulation was seldom seen. The proximal colon, like the small intestine, is evidently under the influence of the vagus. In the distal colon such influence could not be recognized, although the different function of this section of the gut was modified, but did not always alter itself in the same way in response to electrical stimulus.—C. S. Leonard (Courtesy of Biol. Abst.).

QUACKENBUSH, FORREST WARD, PLATZ, BLANCHE RIISING AND STEENBOCK, HARRY.

Rat Aerodysmia and the Essential Fatty Acids. J. Nutrition, 17(2):115-126, 1939.

On a basal diet of purified casein, glucose and salts, supplemented with carotene, calciferol, synthetic B. and riboflavin, rats developed a severe dermatitis which de-

veloped in over 500 animals within 4 to 5 weeks and which took on an acute and a chronic form; complete healing of either was obtained by the adm. of pennut oil or wheat germ oil. By a standardized technique cures were obtained with $\frac{1}{2}$ drop of wheat germ oil, corn oil, or Wesson oil, 10 drops of coconut oil and 25 drops of butterfat. The lesions were not prevented or cured by a supplement of 10% hydrogenated coconut oil. The unsaponifiable fraction from wheat germ oil was devoid of potency. The ethyl esters prepared from the soap fraction contained all of the activity. When the unsaturated fatty acids were fractionally crystallized from acetone, the highest potency was obtained with a fraction separating between -50 and -75° C. One-half drop of ethyl linoleate per day was curative.—Authors (Courtesy Wistar Biol. Serv.).

DIHAYAGUDE, R. G. AND KHADILKAR, V. N.

True Achlorhydria and Anaemia. Indian J. Med. Res., 26(3):705-730, 1939.

A study of 75 cases of achlorhydria by fractional test-meal analysis was made. Majority of the cases showed varying grades of anaemia. To find out whether achlorhydria was true or false subcut. inj. of 0.5 cc. of histamine acid phosphate (B.D.H.) was given after the fasting contents were taken out. 11 out of 75 showed free acid in fasting contents when the test was repeated. 25 showed free acid after histamine stimulation. Out of 75 cases of achlorhydria 39 were found to be cases of true achlorhydria, more than half of these were cases of Addison's pernicious anaemia or subacute combined degeneration of the cord, 4 Witt's anaemia, 3 associated with ankylostom infection and 5 of pellagra. The remaining were single instances of malaria, syphilis, cystitis, asthma and dyspepsia where the achlorhydria was probably accidental.—Authors (Courtesy of Biol. Abst.).

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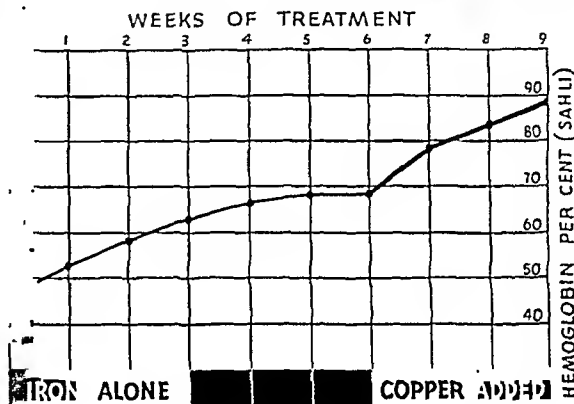


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*Am. J. Med. Scien., 6:182, 1931. Lyon, B. B. Vincent.

**Arch. Int. Med., 38:647, 1926. Am. J. Surg., 7:455, 1929.

Ivy, A. C.
***J. Lab. & Clin. Med., 19:567, 1934. CoTul, F. W.

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nervous system in peptic ulcer in terms of the complete reflex cycle many of the characteristic symptoms and signs as well as sequelae find an explanation. Very striking indeed in many of these cases are the ascending pulse rates which become so rapid that counting is no longer possible; here capillary hemorrhage has occurred in the dorsal motor nucleus implicating the cardiac neurones, destroying their inhibitory effect and leaving the heart entirely to the accelerating effects of the sympathetic innervation. Most important of all, however, is the understanding of a probable reason for many of the

sequelae following recovery from a severe attack of peptic ulcer—the irritable pulse rate, the increased sweating, the signs of "sympathetic imbalance," all point to injury in the parasympathetic centers of the dorsal motor nucleus of the vagus, while quick fatigability, irritability, emotional changes, and alterations of metabolism, sleep and temperature regulation points to injury in the thalamus and hypothalamus. To regard such manifestations as merely neurotic is frequently untrue and injustice may be done by not recognizing an organic handicap.

TURELL, R., MARINO, A. W. M. AND NERB, L.

Observations Concerning Absorption of Sulfanilamide From Large Intestine in Man: An Experimental Study. The Brooklyn Hospital J., 1:90, April, 1939.

In a previous investigation, it was found that sulfanilamide introduced into the rectum of rabbits is rapidly absorbed. In the present communication the results of studies on the absorption of one per cent solution of sulfanilamide from the human colon and rectum are recorded. A series of eight normal individuals who received rectal instillations of one per cent solution of sulfanilamide showed the presence of the drug in the blood. In order to determine whether the drug is absorbed directly from the rectum or colon or whether it must pass to the ileum before being absorbed, the same investigation was repeated in a patient who three years previously had had an ileostomy with exclusion of the colon. It was demonstrated that absorption of sulfanilamide took place from the isolated colon. In another instance direct absorption of sulfanilamide from an isolated human rectal pouch was demonstrated. Sigmoidoscopic studies revealed no apparent changes in the mucous membrane of the rectum and colon as a result of the rectal administration of sulfanilamide. The foregoing experimental studies showed that adequate concentrations of sulfanilamide can be maintained in the blood by means of rectal instillations of one per cent solution of sulfanilamide. The rectal route of administration is recommended when sulfanilamide cannot be given by mouth.

MARINO, A. W. M. AND TURELL, R.

Treatment of Internal Hemorrhoids by Injection: A Study Based on Observations of 5000 Injections. The Brooklyn Hospital J., 1:93, April, 1939.

This study based on 5000 injections, showed that injectional therapy when used with discretion and applied to properly selected cases has a well deserved place in the therapeutics of hemorrhoids. It can be applied to about 40 per cent of all patients with uncomplicated internal piles.

The procedure should be restricted to the treatment of uncomplicated, soft, bleeding, and moderate sized prolapsing, but easily reducible piles. Injectional therapy induces an inflammatory reaction within the interstitial tissue of the hemorrhoidal mass, thereby causing an obliteration of its vessels by thrombosis, which is followed by fibrosis. We are now studying experimentally the various



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successive histologic changes involved, and the fate of the fibrosis.

The contraindications, dangers and the technique of injection are described in detail. Properly performed injections should not result in complications. When any occur they usually are attributed to errors in technic. The patients should be followed for one year or longer. In six per cent of the cases there was a definite recurrence of the internal hemorrhoids. Since injectioanal therapy does not remove the original etiologic factors responsible for the development of hemorrhoids, recurrence can hardly be considered a failure in those instances where the cause was not eliminated.

Comparative studies show that hemorrhoidectomy is still the method of choice. In certain instances where hospitalization is undesirable or when hemorrhoidectomy cannot or should not be performed, injectioanal therapy may be elected. Injectioanal therapy was employed with satisfaction in diabetes mellitus, diabetes insipidus, pulmonary tuberculosis, neurosyphilis, and in patients with hypertensive cardiovascular disease with good myocardial compensation.

Injectioanal therapy may be employed with good chances of success in patients who have mild obstructive lesions of the vesical neck. When the lesion at the bladder neck is progressive in nature, this procedure fails to

relieve bleeding from uncomplicated internal hemorrhoids. In these cases hemorrhoidectomy is also unsuccessful unless the obstructive lesion at the vesical neck is first eliminated. After the enucleation or transurethral resection of the prostate, the edema in this region disappears, and the hemorrhoids, in most instances will regress.

Injectioanal therapy is useful in the early months of gestation. Uren and quinine hydrochloride should not be employed for obvious reasons.

The method of treatment of hemorrhoids by injection is not without danger. Surgical judgment as well as skill are essential, for although the method seems simple, unless one understands the rationale and technic, disappointment and complications may result.

NERR, L., TURELL, R. AND MARINO, A. W. M.

Absorption of Sulfanilamide from Rectum and Colon of Rabbits. The Brooklyn Hospital J., 1:88, April, 1939.

Sulfanilamide administered to rabbits by rectum in the form of solution, suppository or capsules is absorbed rapidly. The rabbits were found to be unsatisfactory animals for this experiment because they frequently expelled all or parts of the chemical. In spite of these difficulties, various amounts of sulfanilamide were found in the blood. The concentration of sulfanilamide in the blood stream was found to be the same in two rabbits when equivalent amounts were first administered orally, and in three days rectally. The possibilities that following rectal administration, the drug may be propelled to the ileum and absorbed from there were considered.

Robert Turell.



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RABINOWITCH, I. M. AND FOWLER, A. F.

Variation of Weight of Dry Feces in Short Period Experiments with a Low Residue-Neutral Ash Diet. J. Nutrition, 16(6):565-569, 1938.

The average daily weight of dried feces of normal individuals on ordinary diets, fluctuated widely, between 25 and 60 gm. per day. Over long periods on a diet constant composition, the average weight of the dried feces fluctuated within a much narrower range. In a series of 20 experiments, the average weight ranged within a few gms. only, even in short period experiments—3 to 20 days—providing the diet was low in residue and produced a neutral ash; the average excretion per day was 21.5 gm. with a standard deviation of 2.1

METHODS FOR QUANTITATIVE ESTIMATION OF THE VITAMINS

1. The Determination of Vitamin D Activity

● About fifteen years ago it was clearly established that there could be present in certain foods or biological materials some substance which possessed antirachitic potency. Subsequently this "antirachitic factor" became known as vitamin D. Today, we know that at least ten sterol derivatives may exert antirachitic effects closely comparable to those of the originally discovered vitamin D (1).

Recognition of the existence of the antirachitic vitamin naturally stimulated investigation of methods whereby this dietary essential could be quantitatively estimated. Steady advances in knowledge of the causes and effects of rickets brought gradual improvements in these methods. Consequently, there are now available several techniques for the quantitative determination of vitamin D in foods or other biological materials.

The first and probably most widely employed method for estimation of vitamin D is by means of the so-called "line test" (2). In this technique as now employed (3), young rats are confined for 18 to 25 days to a diet conducive to development of rickets. These periods of time, with proper handling and confinement of the animals, are sufficient to induce a definitely rachitic condition. The rachitic rats are then properly grouped with respect to negative control groups to receive no supplements to the rachitic ration; positive control or reference groups to receive graded doses of some standard reference material; and "assay groups" to be given graded doses of the material under test. For the next 8 days the animals are fed daily doses of the proper supplement, either assay or reference material. No supplements are fed on the ninth and tenth days.

On the eleventh day the animals are sacrificed and either the proximal end of the tibia or the distal end of the radius or ulna dissected out, sectioned, cleaned and finally

immersed in silver nitrate solution. By double decomposition reaction, silver salts deposit where calcium is present in the metaphysis of the bone. When exposed to light these silver salts are reduced and form a dark line indicating the extent of calcium deposition. The experienced technician can estimate the degree of healing from rickets by the continuity and area of the line. By comparison of the results obtained on the various groups of animals, a quantitative expression of the antirachitic activity of the material under assay may be obtained.

A second method for evaluating vitamin D activity is that involving determination of "bone ash" (4). In this technique, final estimation of the degree of bone calcification—and thus the antirachitic potency of the substance under assay—is made by chemical analysis of specific bones of the experimental animals. A third assay method (5) is that involving roentgenological examination of certain bones. Comparisons of the bone densities of the various experimental animals serve as a basis for estimating the degree of healing from—or prevention of—rickets and hence permit determination of the vitamin D activity of the material under test.

Common foods as they naturally occur can hardly be considered as food sources of vitamin D. However, as exceptions, certain foods of marine origin (6) might be mentioned which consistently contribute small but definite amounts of the antirachitic factor to the diet. In addition, development of various means of fortifying foods with vitamin D—particularly those foods of importance in infant and child feeding—has made available other food sources of the vitamin (7). Among the many varieties of commercially canned foods will be found products of both types, which, when properly used or supplemented, should prove of value in obtaining an adequate intake of vitamin D, particularly by infants and children.

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(1) 1938 J Am Med Assoc 110, 2150.

(2) 1922 J Biol Chem 91, 41.

(3) 1936 The Pharmacopoeia of the United States of America, Eleventh Decennial Revision, 482.

(4) 1923 J Biol Chem 58, 71.

(5) 1924 Ibid 61, 405.

(6) 1928 Biochem J 22, 135.

(7) 1938 J Am Med Assoc 111, 528.

(7) 1937 J Am Med Assoc 108, 206.

We want to make this series valuable to you, so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles. This is the fifty-second in a series, which summarize, for your convenience, the conclusions about canned foods reached by authorities in nutritional research.



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and a probable error of the mean of 0.31.—Author (courtesy of Biological Abstracts).

NEBELL, A. J.

Experimental Gastric Ulcer (Pituitary in Episodes). Arch. Path., 26(5):1988-1998, 1978.

Pituitary injections readily produce gastric and duodenal ulcers in experimental animals (dogs) and these are located in places common to the same lesions in man. The direct observations of the mucosa, together with the histological observations of the progression of ulcer formation from the very beginning to the end states,

definitely reveal the role of vascular dysfunction in ulcer formation. The vascular interference in local nutrition is the primary factor of these pathological developments. Depending on the constitutional type, on vascular instability and on the endocrine balance, on seasonal variation, on emotional situations, trauma, and meteorological factors, vascular incoordination may evidently be of sufficient intensity of duration to lead to prolonged local anoxia with resulting development of gastric and duodenal ulcers. Peptic ulcers should therefore be regarded as a local expression of vascular dysfunction inherent in con-

stitutional types unable to withstand the demands of the organism for adjustment to unusual environmental situations.—A. J. N. (courtesy of Biological Abstracts).

ALSTED, G.

On the Increasing Frequency of Gastro-Intestinal Hemorrhages. Acta Med. Scand. Suppl., 89, 332-336, 1 fig., 1938.

Dyspeptic disorders show increasing frequency among males, with increasing severity, and tendency to gastro-intestinal hemorrhage.—J. F. W. (courtesy of Biological Abstracts).

ASCHAM, LEAH, SPEARS, MARY AND MADDOX, DOROTHY.

The Availability of Iron in Various Foods. J. Nutrition., 16(5):425-436, 1938.

The ability of certain foods to promote Hb regeneration in young rats rendered anemic by prolonged feeding on whole milk was studied in order to measure the availability of the Fe in these foods. Canned collards and turnip greens induced greater rises in Hb when both the leaves and liquid were fed than did the dried forms of these greens. The Fe in canned turnip green leaves alone was less available than that in the dried leaves. The various dried foods studied fell into the following descending order: blackeyed peas and spinach, turnip greens and kale, collards and mustard, head lettuce, and lastly tendergreen and leaf lettuce. For these foods no relation was found between their available Fe content determined by bioassay and their ionizable Fe content determined chemically by the α , α ' dipyrrolyl method.—(Courtesy Biol. Abst.).

SANSUM, W. D.

The Favorable Influence of Adequate (Higher) Carbohydrate and Lower Fat Diets on the Arteriosclerosis Problem Associated with Diabetes Mellitus. Acta Med. Scand. Suppl., 90:89-86, 1938.

Higher carbohydrate, lower fat diets, restored diabetic patients to a more normal state of health, and apparently lowered the incidence of arteriosclerosis. The problem is far from settled but such diets are feasible and have many other advantages aside from their probable relation to arteriosclerosis.—J.F.W. (Courtesy Biol. Abst.).

RAHMAN, LINCOLN, RICHARDSON, HENRY B. AND RIPLEY, HERBERT S.

Anorexia Nervosa with Psychiatric Observations. Psychosom. Med., Vol. 1, pp. 335-365, July, 1939.

The frequency with which anorexia nervosa is mistakenly diagnosed as

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Science calls the common banana "Musa Sapientum," which means fruit of the Wise Men. According to an ancient legend, the sages of India reposed in the shade of the banana plant and refreshed themselves with its luscious fruit.

INTERESTING BANANA FACTS

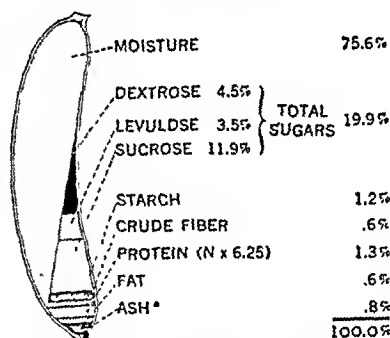
THE ripe banana contains about 20% sugars with nearly 5% other solids consisting of protein, fat, pectins, minerals, vitamins and small amounts of starch and fiber. Its semi-solid texture must hence be attributed to the way in which moisture, sugars and the other constituents are held in a delicate meshwork of cellulose and pectin substances, and not to low moisture or high fat content. The sugars present are sucrose, levulose and dextrose. The two simple sugars account for about 40% of the total sugars.

The key to the varied usefulness of the banana is to be found in its composition. Special points stand out as qualifying it for inclusion in special types of diets. These are summarized in outline form below:

PROPERTIES OF RIPE BANANA PULP

PROPERTIES OF RIPE BANANA PULP	MAKE IT OF VALUE IN
Readily assimilated sugars (along with vitamins, minerals and fiber).....	Infant Feeding
Caloric value (along with vitamins and minerals).....	Malnutrition
Satiety value and low fat (along with vitamins and minerals) ..	Reducing Diets
Alkaline residue ..	Combating Acidosis
Vitamin content ..	Preventing Deficiency Diseases
Soft texture and blandness (with carbohydrates, vitamins, minerals, pectin and fiber).....	Intestinal Disturbances
	Normalizing Colonic Function
	Convalescent Diets

PROXIMATE COMPOSITION RIPE BANANA PULP



* Contains important minerals including calcium, copper, iron and phosphorus

VITAMINS IN BANANAS (Units per Ounce)

International	Sherman
A-71 to 95	B-4 to 5
C-57	G-10

LITERATURE ON REQUEST

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Simmonds' disease warrants reading this paper.

Characterizing this entity as a neurosis with psychosomatic manifestations, the authors present twelve patients. It is apparent that endocrine manifestations appear secondary to the starvation which the body undergoes. Obsessive, compulsive, anxiety, and depressive features are prominent.

The physical findings are those found in starvation, including "emaciation, dry, scaly skin, cold bluish extremities, amenorrhea, atrophic type of vaginal smear, subnormal temperature, slow pulse and low blood

pressure. Common personality characteristics were stubbornness, meticulousness, parsimony, ambitiousness, seclusiveness, shyness, dependence on others and difficulty in making friends. The patients' own statements indicated an avoidance of assuming normal sexual relationships. Frequently excessive interest by a parent in the function of the intestinal tract had been impressed on the patient in early life."

The major course of the treatment is regulation of regime plus psychotherapy.

H. H. Lerner, Boston, Mass.

THE AMERICAN PROCTOLOGIC SOCIETY

At its recent meeting in Brooklyn, Dr. Martin S. Kleckner, of Allentown, Pa., was elected President of the Society to succeed Dr. Dudley Smith of San Francisco.

The following other officers were elected:

Dr. Martin Marino, Brooklyn, Vice-President,

Dr. Frederick B. Campbell, Kansas City, Treasurer,

Dr. Cecil Gaston, Birmingham, and Dr. Walter Fansler, Minneapolis, Counsellors,

Dr. Harry E. Bacon, Philadelphia, Editor,

Dr. Curtice Rosser, Dallas, Secretary.

The next annual meeting will be held in Richmond, Virginia, on June 9, 10 and 11, 1940, with Dr. E. H. Terrell as Chairman of Arrangements.

The following were elected to Fellowship:

Senior Fellows:

Dr. Alois Baehman Graham,

Dr. John Lemuel Jelks,

Dr. Collier Ford Martin.

Fellows:

Dr. Robert A. Searborough,

Dr. Warren W. Green,

Dr. Wm. K. McIntyre,

Dr. Jerrold P. Nesselrod.

Curtice Rosser, Sec'y.

CONDON, PALMER AND BURGESS, ALEXANDER M.

Clinical Experience with 95 to 98 Per Cent Oxygen in the Treatment of Abdominal Distention and Other Conditions. The New Eng. J. of Med., Vol. 221, pp. 299-302, Aug. 24, 1939.

The use of oxygen in the treatment of abdominal distention is reported in a series of forty cases. Twenty-five of the patients received definite benefit, five questionable benefit, and ten were uninfluenced. Cases with emphysema all had satisfactory results.

The method is considered life saving in severe abdominal distention such as is seen in pneumonia, typhoid fever, and post-operative peritonitis.

H. H. Lerner, Boston, Mass.

MCCANCE, R. A., WIDDOWSON, E. M. AND VERDON-ROE, C. M.

A Study of English Diets by the Individual Method. III. Pregnant Women at Different Economic Levels. J. Hyg., 38(5): 596-622, 1938.

Different economic levels did not affect the diets of 120 subjects in respect to the intake of calories, fat and carbohydrate, whereas the intakes of protein, animal protein, Ca, P, Fe and Vitamin B rose convinc-



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"Proceedings of the Society for Experimental Biology and Medicine", 40:157, 1939.

Knox Gelatine is high in certain amino acids, which are precursors of muscular creatine. Thus, by increasing the phosphocreatine content of the muscle, Knox Gelatine increases its chemical store of potential energy.

The gelatine used in this study was plain Knox Gelatine (U.S.P.) which assays 85% protein and which should not be confused either with inferior grades of gelatine or with sugar-laden dessert powders, for these latter products will not achieve the desired effects. When you desire pure U.S.P. Gelatine, be sure to specify KNOX. Your hospital can get it on order.

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ingly with income. A rise in spending power led to increased consumption of milk, fruit, vegetables and meat, and to a decreased consumption of bread and total cereals. Women taking the better diets were, on the average, significantly taller and less anaemic than those on the poorer diets. A comparison of the diets of the well-to-do women with the dietary requirements suggested by the League of Nations and other authorities suggests that the calorie standard has been set too high. The intake of Ca was suboptimal throughout and the diets of the poorer women were deficient in many

respects. — C.M.D. (Courtesy Biol. Abst.).

GOORLEY, J. T. AND LEE, C. O.

A Study of Enteric Coatings. J. Am. Pharm. Assoc., 27(5):379-384, 1938.

The following materials were used in coating capsules: keratin; salol; stearic acid; combinations of stearic acid with salol, paraffin, wax, ceresin, glycoesterin, lauric acid, palmitic acid, myristic acid; sandarac; shellac; collodion; tolu; benzoin; lacquers; albuminoids; waxes; formaldehyde-gelatin; castor oil; shellac, and alco-

hol mixture. Of these studied, only the last-named gave evidence of disintegrating in the intestine within a reasonable time and of not being damaged by passing through the stomach. Best results followed administration on an empty stomach about 1 to 2 hours before meals. Successful enteric coatings must possess other properties than solubility simply in alkaline media. Small capsules appear to pass out of the stomach much more uniformly and within a shorter period of time than do larger capsules. — G.M.H. (Courtesy Biol. Abst.).

ANSON, M. L.

The Estimation of Pepsin, Trypsin, Papain and Cathepsin with Hemoglobin. J. Gen. Physiol., 22(1):79-91, 4 figs., 1938.

The procedures were completely described and the activity units defined. Directions for constructing a curve relating activity units to color values of digestion products were given.—E. S. (Courtesy Biol. Abst.).

BEST, C. H. AND RIDOUT, JESSIE H.

Under Nutrition and Liver Fat. J. Physiol., 94(1):47-66, 4 figs., 1938.

Many expts. on large groups of rats indicate that accumulation of fat in the liver during fasting is an extremely variable phenomenon; under the conditions of these expts., male rats usually do not exhibit an increase in total liver fat although there may be a slight rise in the %, while large female rats usually exhibit some increase.—T. C. B. (Courtesy Biol. Abst.).

FRANKLIN, D. J. AND MAHER-LOUGHAN, G. P.

The "Circular" Musculature of the Small Intestine. J. Physiol., 94(3):426-429, 1938.

Experimental evidence is given, which supports Carey's view that there is a close spiral arrangement of muscular fibres in the small intestine of certain spp. The direction of the spiral is anti-clockwise, viewed from above (stomach end of the intestine). The physiological implications are discussed.—T. C. B. (courtesy of Biological Abstracts).

BORST, J. G. G.

The Cause of Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage From Peptic Ulcer. Acta Med. Scand., 97(1/2):68-88, 1938.

The hyperazotemia following massive gastro-intestinal hemorrhage depends on the increased formation of urea from the blood in the bowel. The hyperazotemia leads to relative poly-

PROCHOLON

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BEST,¹ in a study of biliary disease, found that much of the postoperative distress after gall-bladder removal was due to (a) spasm of the choledochal sphincter and (b) mechanical obstruction due to "remaining stone, mucous plug, inspissated bile, or blood clot." Both conditions resulted in a back pressure of bile throughout the intricate duct system within the liver.

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¹ Best, R. Russell: *Rocky Mtn. M. J.* 36:319 (May) 1939.

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uria, and the urea concentration (45-60 g. per l) remains maximal until the blood volume is restored. If shock develops, both diuresis and maximum urea concentration fall and the blood urea rises further. The urea clearance may be the best measure of the severity of the shock. Post-hemorrhagic blood dilution is retarded by high diuresis, with a restricted fluid intake, by low blood albumin, and capillary damage. While post-hemorrhagic dilution is progressing, the kidneys excrete neither Na nor chlorides; if NaCl is given the plasma NaCl increases above the normal. The retention of salt and increased excretion of K form part of a regulating mechanism for restoring the normal filling of the arterial system.—J. F. W. (courtesy of Biological Abstracts).

PATTERSON, CHARLES A., SMITH, ERMA AND HALE, H. B.

Food Intake and Gastro-Intestinal Motility in the Albino Rat During Chronic CO Asphyxia. Proc. Soc. Exp. Biol. and Med., 39(3):509-511, 1 fig., 1938.

Albino rats exposed daily for one hour to 0.34 per cent CO consumed 23 per cent less food during a period of about 2 months than their litter mate controls. If treated with CO immediately after eating a test meal, peristalsis was inhibited and the ingestion time increased about 22 per cent. — Authors (courtesy of Biological Abstracts).

BANKS, BENJAMIN M. AND BARRON, LOUIS E.

The Phenolphthalein Test in the Diagnosis of Gastro-Intestinal Disease. The New Eng. J. of Med., Vol. 221, pp. 296-299, Aug. 24, 1939.

Fifty-two patients with intrinsic lesions of the gastro-intestinal tract and a hundred and fifty-one controls were examined by a modification of the Woldman phenolphthalein test to determine the presence of defects in the mucosa of the intestinal tract.

One fourth of the cases with alimentary disease failed to give a positive test, while one-sixth of the control cases gave a false positive. The results therefore indicate a wide range of error for the test thus limiting its usefulness.

H. H. Lerner, Boston, Mass.

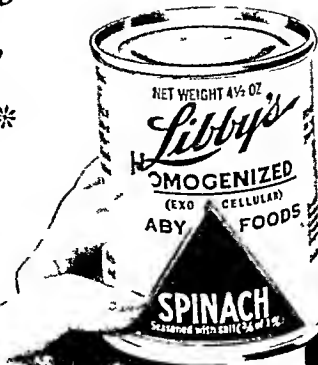
SEYMOUR, W. B., SPIES, TOM DOUGLAS AND PAYNE, WARREN.

The Gastric Secretion in Chronic Alcoholic Addiction. J. Clin. Invest., 18(1):15-18, 3 figs., 1939.

The gastric secretion in 40 chronic alcoholic addicts was studied, histamine being used as a secretory stimulant. There was no clinical evidence of vitamin deficiency, and no labora-

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Energy
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Strained
Vegetables
— 1 minute



Homogenized
Vegetables
— 1 minute



Strained
Vegetables
— 37 minutes



Homogenized
Vegetables
— 36 minutes



Strained
Vegetables
— 62 minutes



Homogenized
Vegetables
— 61 minutes



Strained
Vegetables
— 154 minutes



Homogenized
Vegetables
— 79 minutes

For full summary of these experiments—
reported in September issue of *The Journal-
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tory evidence of anemia. The results show an average diminished secretory volume and an average diminished acidity but the peptic activity of the gastric juice was apparently unimpaired. Comparison of the incidence of the achlorhydria with the expected normal incidence for the various age groups shows a considerable increase of achlorhydria over normal. Comparison of the incidence of achlorhydria in our series with a series of alcoholics with polyneuritis in which histamine was used as a secretory stimulant shows that the per cent with achlorhydria was much higher in the latter group.—W. B. S. (courtesy of Biological Abstracts).

STEWART, H. L. AND CANTAROW, A.

Experimental Carbon Tetrachloride Poisoning in the Cat. II. The Influence of Ligation of Single Bile Ducts. Arch. Path., 26(6):1121-1130, 1938.

In adult cats the subcutaneous injection of CCl_4 is followed by the development of characteristic regressive and regenerative phenomena in the central zones of the hepatic lobules. In cats subjected to ligation of single hepatic ducts 2 weeks prior to injection of CCl_4 the hepatotoxic effect of this poison is distinctly less marked than in previously normal animals. This difference is strikingly evident in both polygonal and Kupffer cells. Except at 2 and 8 days following injection, the regressive changes are of approximately equal severity in obstructed and nonobstructed lobules; at those stages the damage is distinctly more marked in the latter. The morphological differences between the 2 groups of animals are reflected in the functional activity. Abnormalities in bilirubinemia, retention of bromsulphalein and urobilinuria are less marked in those with ligation of single bile ducts than in previously normal animals. The possible causes of these differences are discussed.—A. C. (courtesy of Biological Abstracts).

MEULENGRACHT, E.

Histologic Investigation Into the Pyloric Gland Organ in Pernicious Anemia. Am. J. Med. Sci., 197(2):201-214, 6 figs., 1939.

In earlier works by the author it was shown that the antianemic factor of the stomach (Castle's intrinsic factor) must be secreted by the pyloric glands and the histologically indistinguishable Brunner's glands. Now stomach and duodenum from 8 pernicious anemia patients have been subjected to a histologic investigation. Gastritis changes in the fundus portion with atrophy of the glands and disappearance of parietal and



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chief cells were found in all 8 cases. But the gastric changes were less pronounced in the pyloric portion, and the glands seemed relatively well preserved; no histologic changes could be demonstrated in Brunner's glands. How the above finding, which at first sight is rather surprising, can be brought into line with the present conception of the pathogenesis of pernicious anemia is discussed.—E. M. (courtesy of Biological Abstracts).

AUER, JOHN AND SEAGER, LLOYD D. *Functional Activity of Pancreatic Ampulla in Rabbit. Proc. Soc. Exp. Biol. and Med., 39(3):542-543, 1938.*

In rabbit under barbital narcosis, the intraven. inj. of a crude secretin mixture containing histamin causes a series of contractions and relaxations beginning at the junction of the pancreatic duct with the ampulla. The contractions gradually increase in strength and frequency until one sweeps over the entire ampulla. Each contraction is followed by a relaxation. A complete contraction may last 1-2 seconds. The relaxation generally proceeds from the distal end of the ampulla to the duct. The number of contractions may reach 10 per minute after one injection and they persist in decreasing numbers some 10 minutes. The same events may be seen in the bile papilla which in the rabbit is about 15 cm. distant from the pancreatic ampulla.—J. A. (courtesy of Biological Abstracts).

ELTON, NORMAN W.

The Relation of the Liver to Nutrition, with Special Reference to the Nervous System. II. Section on Clinical Pathology of the Liver. Rev. Gastroenterol., 5(2): 208-214, 1938.

A discussion of different liver function tests.—G. H. Chapman (courtesy of Biological Abstracts).

BINET, M. E.

Hepatic Insufficiency in Chronic Colitis. Rev. Gastroenterol., 5(3): 287-292, 1938.

Colitis frequently develops into biliary infection and hepatic insufficiency. The most serious sequel in malnutrition, often hepatic in origin. G. H. Chapman (courtesy of Biological Abstracts).

ALT, H. L., CHINN, H. AND FARMER, C. J.

The Blood Plasma Ascorbic Acid in Patients with Achlorhydria. Am. J. Med. Sci., 197(2):229-233, 1939.

Evidence in the literature suggests that achlorhydria might be a predis-

posing factor in the production of Vitamin C deficiency. Determinations of the reduced ascorbic acid content of the plasma were made in 44 patients with achlorhydria. This group consisted largely of patients with pernicious anemia or achlorhydric anemia in remission. The mean value of 0.57 ± 0.02 mg. ascorbic acid per 100 cc. plasma obtained in the achlorhydric patients was significantly lower than the mean value of 0.79 ± 0.03 mg. per 100 cc. obtained in 24 control cases. This difference was not related to variations in the diet. Various experiments suggest that acidity and malabsorption may explain, in part at least, the low plasma ascorbic acid observed in the achlorhydric patients.—H. C. (courtesy of Biological Abstracts).

LOEW, E. R. AND PATTERSON, T. L. *The Reflex Influence of the Lower Portion of the Large Intestine on the Tonus and Movements of the Empty Stomach. Quart. J. Exp. Physiol., 28(4): 305-314, 3 figs., 1938.*

Distention of an intrarectal balloon in gastric fistularized dogs produces inhibition of the tonus and motility of the empty stomach. Small amounts of pressure (6-18 mm. of Hg.) generally produce definite effects, the duration and degree of this inhibition being somewhat dependent on the magnitude of the intrarectal pressure. Recovery usually occurs even while the pressure is maintained in the rectum although this pressure may decrease when the rectum adapts itself. Dog's undiluted gall bladder bile produces similar effects when introduced into the rectum in such a manner that the animal is undisturbed during the administration. Glucose and physiological saline solutions are negative.—Authors (courtesy of Biological Abstracts).

STEWART, H. L. AND ANDERVONT, H. B.

Pathologic Observations on the Adenomatous Lesion of the Stomach in Mice of Strain 1. Arch. Path., 36(5):1009-1022, 1938.

A spontaneous adenomatous lesion in the pyloric chamber of the stomach in mice of strain 1 is described and illustrated. The lesion occurs in virtually all mice of both sexes of this strain and is the chief cause of death in mice of this strain. Mice of strain 1 are known to die at a relatively early age. The lesion is characterized by an adenomatous, hypertrophic, hyperplastic overgrowth of the glandular rugae of the pyloric mucosa; degeneration and infiltration

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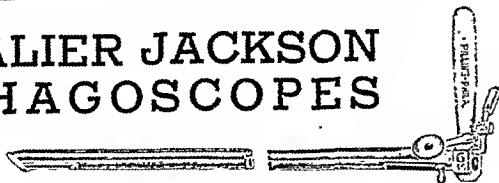
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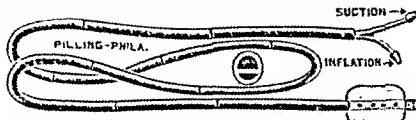
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by inflammatory cells were present together with development of atypical epithelium with limited penetration into the deeper gastric wall and blood vessels. Although histologic studies reveal certain features that are somewhat suggestive of malignant growth, there are contradictory criteria, such as the symmetrical development of the process and the absence of metastases, unlimited local spread, extensive ulceration and destruction.—Authors (courtesy of Biological Abstracts).

HESLOP, T. S.

The Hypothalamus and Gastric Motility. Quart. J. Exp. Physiol., 28(4):335-340, 4 figs., 1938.

The hypothalamus was stimulated using Souttar machine for localization and Thyratron valve stimulator. Gastric motility was recorded by X-ray. Stimulation of supra-optic group of nuclei caused marked increase in rate and depth of peristalsis, tonic contraction of pyloric antrum and a very rapid passage of the barium paste into the intestine. Stimulation of mammillary group caused a momentary relaxation of the pyloric antrum only. Experiments were all carried out on 2½ kgm. female cats.—T. S. H. (courtesy of Biological Abstracts).

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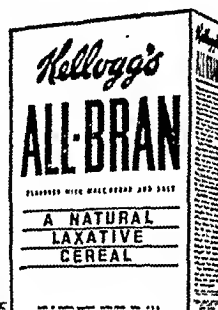
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Intubation Studies of the Human Small Intestine:

XVII. The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon*

By

KENDALL A. ELSOM, M.D.

and

J. L. DROSSNER, M.D.†

IN spite of the well established pharmacologic observation that atropine depresses the motor function of the bowel its clinical use for that purpose has often been disappointing. We have consequently taken advantage of the technique of intestinal intubation, as developed in this clinic (1), and as previously employed by Abbott and Pendergrass (2) in a study of morphine, to determine objectively the effects of atropine and belladonna on the motor functions of the small intestine and colon of man. Both drugs produced a marked and lasting decrease in tone and motor activity of whatever portion of the tract was studied.

METHODS AND SUBJECTS

As previously described (2) the apparatus was introduced under fluoroscopic guidance to any desired portion of the tract. The balloon was then inflated with approximately 40 cc. of air under 10-12 cm. of water pressure and connected with a spirometer type of volume recorder which activated a writing lever. In some instances a suspension of barium was introduced to permit simultaneous fluoroscopic observation of the calibre and motor activity of the bowel immediately proximal or distal to the inflated balloon. The method employed in these experiments has limitations discussed by Abbott (2). If the balloon enters a constricted portion of the gut, or is impinged upon by a bolus of intestinal contents the writing lever may indicate an increase in tone which is fictitious. Simultaneous fluoroscopic study usually discloses the fact, however, and therefore serves as a control of this part of the method. No technical errors now recognized produce an apparent fall in tone.

Except for 3 individuals who had abnormalities considered suitable for study all the subjects were without demonstrable gastro-intestinal disease. Two of the three showed small intestinal hypermotility and hyper-tonicity by roentgen examination and a third had ulcerative colitis for which an ileostomy had been performed. This latter subject provided an opportunity for simultaneous intubation through the ileostomy opening of the terminal ileum and the colon. In all subjects control tracings of intestinal activity were obtained before atropine sulphate was injected hypodermically. In a few instances atropine or belladonna was administered orally.

ACTION ON THE DUODENUM

Eight observations were made on 5 subjects. The control tracings from the normal duodenum have two

chief characteristics: The intestinal tone is high and the motor activity is great. Two types of waves are recorded as a rule, large peristaltic waves occurring every minute or two and lasting approximately a minute, on which are superimposed frequent small undulations produced by rhythmical contractions.

Administration of atropine sulphate was followed (Fig. 1) in 10 to 15 minutes by a gradual fall in intraduodenal tone. The large peristaltic contractions were altered simultaneously, often becoming more pronounced as the tone decreased, then gradually diminishing in size and frequency and ultimately disappearing. The small rhythmical waves were decreased in size though usually not in frequency. This effect of atropine was fully developed within 20 minutes

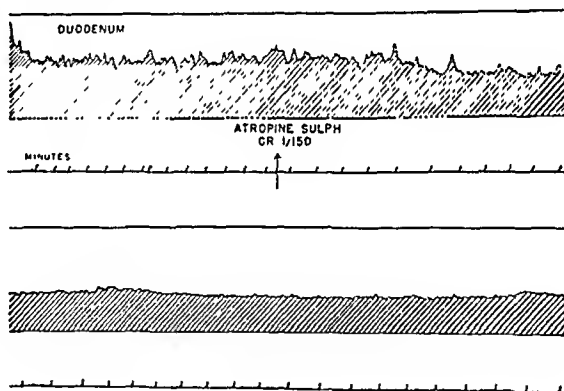


Fig. 1. The effect of atropine on the duodenum. In this and the following figures the upper horizontal line represents the position of the writing lever when the balloon is empty, the base line its position when the balloon contains 40 cc. of air. Time in minutes.

after the injection, and lasted for 1 to 2 hours. Recovery was gradual, with first an increase in size of the small undulations, then the appearance of peristaltic waves and finally an increase in tone.

ACTION ON THE JEJUNUM AND ILEUM

The results of 6 experiments on the jejunum and 3 on the ileum are here considered together since the tracings obtained from these portions of the bowel are similar to each other and rather different from those obtained from the duodenum. In the control tracings taken from these portions of the bowel the high tonus and the marked motor activity which characterize the duodenum diminish progressively as the balloon descends into the more distal segments of the small bowel. The large, relatively infrequent peristaltic

*From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania. Presented in abstract before the forty-second annual meeting of the American Gastro-Enterological Association, Atlantic City, May 3, 1939.

†Smith, Kline and French Fellow in Gastro-Enterology.

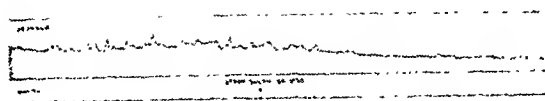


Fig. 2. The effect of atropine on the jejunum.

waves characteristic of the duodenum are inconspicuous in tracings from the jejunum. The small, rhythmic undulations are often the only evidence of motor activity. The effects on the jejunum and ileum produced by atropine were perhaps less striking than those on the duodenum but were no less definite. Fig. 2 shows a representative tracing obtained from the upper jejunum of a normal subject. The first detectable effect was a moderate decrease in intestinal tone. The character of the waves then gradually changed. The larger peristaltic waves decreased and ultimately disappeared, while the rhythmical contractions became smaller, but increased in frequency. The effect of atropine on the ileum in normal subject is seen in Fig. 3. In this instance a suspension of barium had been introduced proximal to the inflated balloon. This procedure altered the type of control record normally obtained from this section of the gut. Large con-

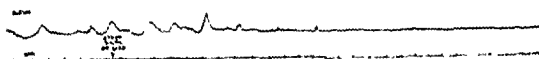


Fig. 3. The effect of atropine on the ileum.

traction waves on which small undulations were superimposed occurred every 1 or 2 minutes and lasted approximately 1 minute. The effect of atropine is clearly apparent. Ten minutes after its injection the tracing was a straight line, except for small, rapid rhythmical waves.

Fig. 4 shows a tracing from the jejunum of a patient, (Mrs. E. R.) whose case history is summarized below. It is abnormal in two respects: the tonus is higher than that customarily found in the jejunum, and the motor activity, with fairly large peristaltic waves, is unusually great. The effect of atropine (0.6 mg.) was striking. A decrease in tonus occurred within 10 minutes after the injection while the peristaltic waves were as large or larger than those in the control period. Within 20 minutes after the injection, the peristaltic waves were absent and the small undu-

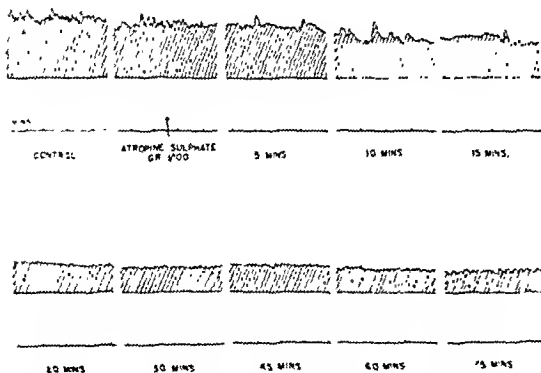


Fig. 4. The effect of atropine on the jejunum of a subject with small intestinal hypermotility and hyper-tonicity.

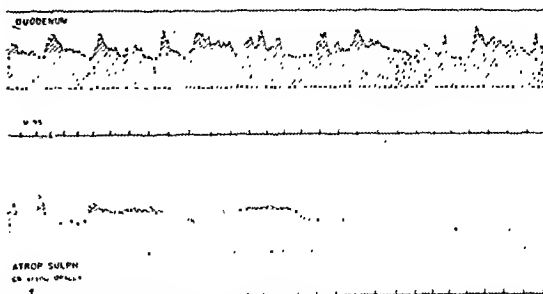


Fig. 5. The effect on the duodenum of atropine administered orally.

lations were greatly decreased in size. Seventy-five minutes after the injection the latter waves had increased in prominence, but peristalsis was still absent and the tonus was greatly diminished.

ACTION ON THE COLON

Four observations were made. In 2 normal subjects the effects were only slight, consisting in a decrease in tone and reduction in motor activity. In these two instances the colon was relatively inactive during the control period and interpretation of the effects of

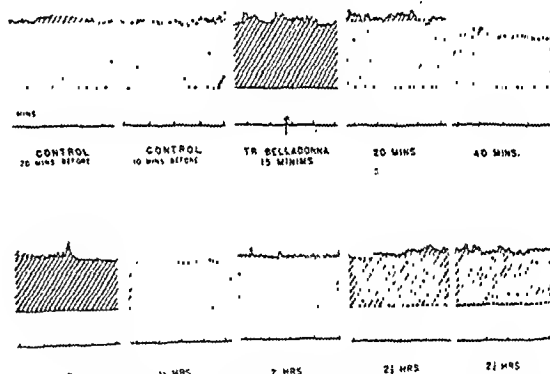


Fig. 6. The effect on the jejunum of Tr. Belladonna administered orally.

atropine was difficult. In the subject with ulcerative colitis the contractions of the colon were abnormally frequent and here the anti-spasmodic action of atropine was clearly apparent. Fig. 7 shows the record obtained from a patient with partial obstruction in the sigmoid region. The control tracing, obtained from the cecum, records frequent large contraction waves which expelled most of the air from the balloon. No such waves appeared after the administration of

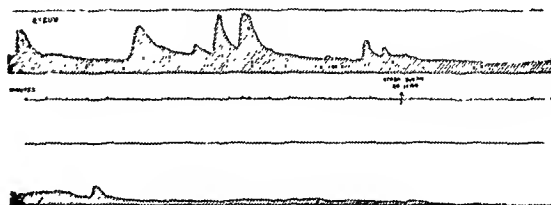


Fig. 7. The effect of atropine on the colon of a subject with partial colonic obstruction.

atropine (0.4 mg.) and the tonus was definitely diminished.

EFFECTS OF ORAL ADMINISTRATION

Atropine sulphate (Fig. 5) and tincture of belladonna (Fig. 6) orally administered produced effects qualitatively similar to those already described for hypodermic injection. The effects were slower in onset, appearing as late as 30 minutes after administration of the drug, and were less marked and less prolonged than from a similar dose administered subcutaneously.

DURATION OF ACTION

The decrease in the peristaltic and rhythmical contractions produced by 0.4 to 0.6 mgm. of atropine sulphate persisted as a rule for 1½ to 2 hours, with gradual return to normal. The effect on intestinal tone was more lasting. In Fig. 6 for example, the tone was still decreased 2 hours after administration of the drug although the contraction waves had returned to their normal size. Because of lack of time most of the observations had to be discontinued while the tone was still abnormally low.

THE EFFECT OF ATROPINE ON SMALL INTESTINAL MOTILITY

The marked decrease in motor activity observed in all portions of the intestine after atropine prompted a study of the rate of passage of the usual barium meal through the small bowel. It is generally agreed that atropine delays gastric emptying (3). Since the rate at which barium leaves the stomach in part determines the speed of its propulsion through the small intestine, the factor of gastric emptying was eliminated as follows: A normal subject was intubated with a Rehfuß tube, the tip of which was observed to lie

in the third portion of the duodenum. In an effort to simulate conditions of normal gastric emptying 175 cc. of a barium suspension were introduced into the duodenum in 7 divided doses of 25 cc. each, injected at 15 minute intervals. The rate of passage of the meal was carefully determined by frequent fluoroscopic examinations. One week later the procedure was repeated under identical conditions except that atropine sulphate (0.4 mgm.) was injected subcutaneously 10 minutes before the introduction of the barium, and 0.2 mgm. was injected 1 hour and 45 minutes following it. Table I indicates the observed differences in motility. The following observation of the effect of atropine in a patient with abnormally rapid small intestinal motility appears to be of practical value:

E. R. (No. 39-37, 955) a white woman, aged 50, complained of diarrhea of 12 years duration. She passed from 5 to 10 stools daily. Flatulence and mild abdominal pain often preceded the passage of the stools, which were liquid or semi-solid. Tenesmus was marked. She was a chronic invalid because of marked asthenia.

Physical examination was negative. Hemoglobin was 74 per cent (Sahli). Extensive laboratory tests were negative. Proctoscopic examination and repeated stool examinations revealed nothing of significance.

Gastro-intestinal roentgen examination disclosed a hypertonic small intestinal pattern with marked hypermotility. At a second examination 3 days later, atropine sulphate (0.4 mgm.) was administered hypodermically 7 minutes before the barium was swallowed, and the dose repeated in 2 hours. The resulting delay in gastric emptying time, the decreased small intestinal motility and the altered pattern are illustrated in Fig. 8.

Twenty drops of tincture of belladonna were administered therapeutically 3 times daily. The diarrhea immediately ceased, one or two formed stools being passed daily, and she stated that she had not felt so well for 10 years. For a two day period, when she was unable to obtain the drug, the diarrhea reappeared, only to disappear when medication was resumed.

DISCUSSION

The effects produced by atropine in the human small intestine and colon are definite. Under the conditions of our experiments the tone is lessened, the muscular contractions are diminished, and, as a result, intestinal motility is decreased. The results were uniform and dependable. In 21 observations the action was marked in 14, moderate in 8, slight in 1, and absent in only 1. These results are in general agreement with evidence derived from the small intestine of animals (4), and the stomach (5, 6) and colon (7) of man.

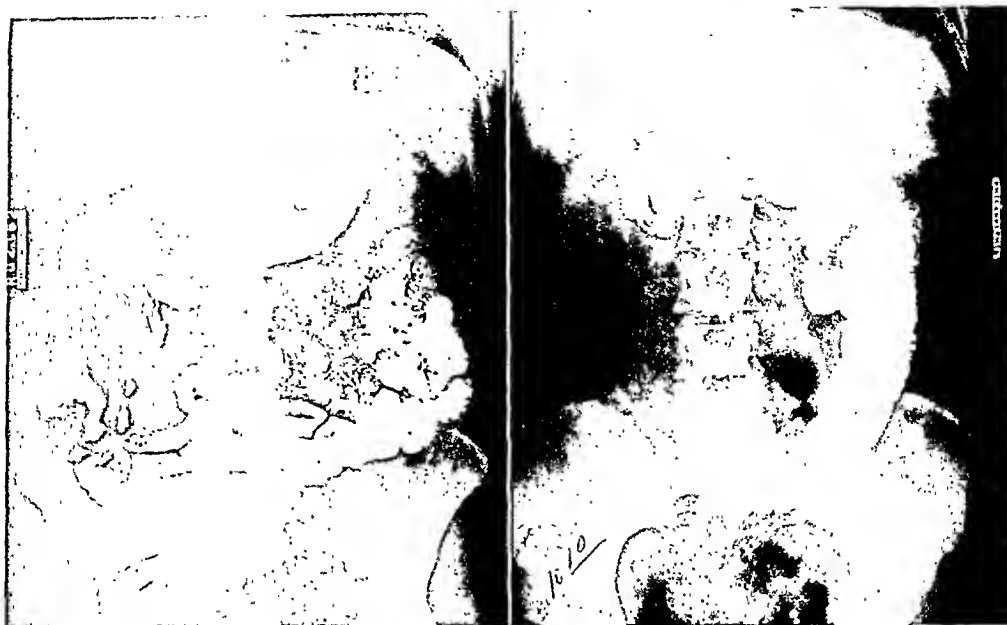
The statement of Cushny (8) that "small (therapeutic) doses of atropine appear to arrest only certain abnormal violent forms of contraction" has not been borne out in our experiments on man, since both abnormal contractions and those observed in the normal bowel were equally affected. The statement of Bastedo (9) that "in doses usually employed by mouth or permissible for any continued treatment, atropine and belladonna are practically without effect on the secretory and motor functions of the stomach" cannot be applied to the small intestine and colon.

While it is true that a balloon occluding the bowel creates an abnormal situation it is impossible to say whether it reproduces any observed clinical disturbances. This uncertainty, however, does not, in our opinion, invalidate the general conclusion that the ob-

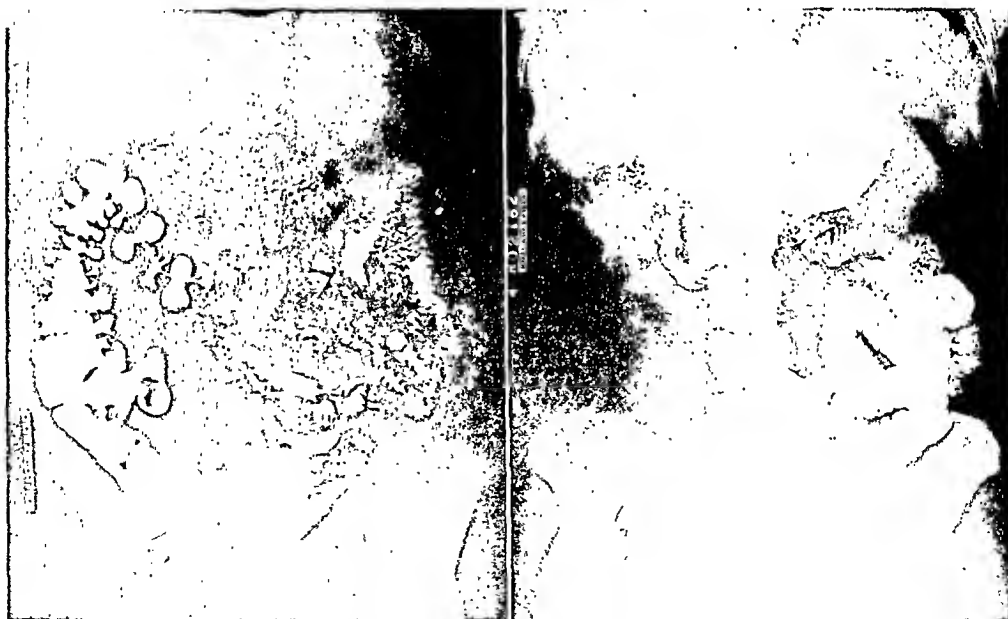
TABLE I

Small intestinal motility before and after the injection of 0.4 mgm. of atropine sulphate

Hours After Introduction of Barium Into Duodenum	The Position of the Barium Meal	
	Without Atropine 2/18/39	With Atropine 2/25/39
½	Chiefly in the upper jejunum.	Entire meal in first few inches of jejunum.
1	In ileal loops situated in pelvis and right lower abdominal quadrant.	Entire meal in duodenum and first two jejunal loops.
1½	Position of head of column not materially changed, most of the barium in mid-jejunum.	Head of the meal in distal jejunum. Most of barium in proximal jejunum.
2	No appreciable change in past half hour.	No appreciable change in the past half hour.
2¾	Head of meal at hepatic flexure of colon. Most of barium in terminal ileum. Observations discontinued.	No appreciable change.
3		No appreciable change.
4		Most of barium in proximal loops of ileum, none in loops situated in pelvis.
5		All of the barium now in the lower ileum, head of column just entering terminal ileum.
5½		Head of column has just reached the cecum.



A



B

served decrease in both tone and muscular activity of the intestinal tract produced by doses of atropine which are well tolerated can properly be expected to produce useful results.

CONCLUSIONS

Atropine sulphate and tincture of belladonna have been administered to normal subjects and patients

with gastro-intestinal disease and their effects on the small intestine and colon studied by means of intestinal intubation combined with fluoroscopy.

In therapeutic doses they produce definite and prolonged effects on the small bowel and colon consisting of a marked decrease in tone and in peristaltic activity and of a less striking effect on rhythmical contractions.

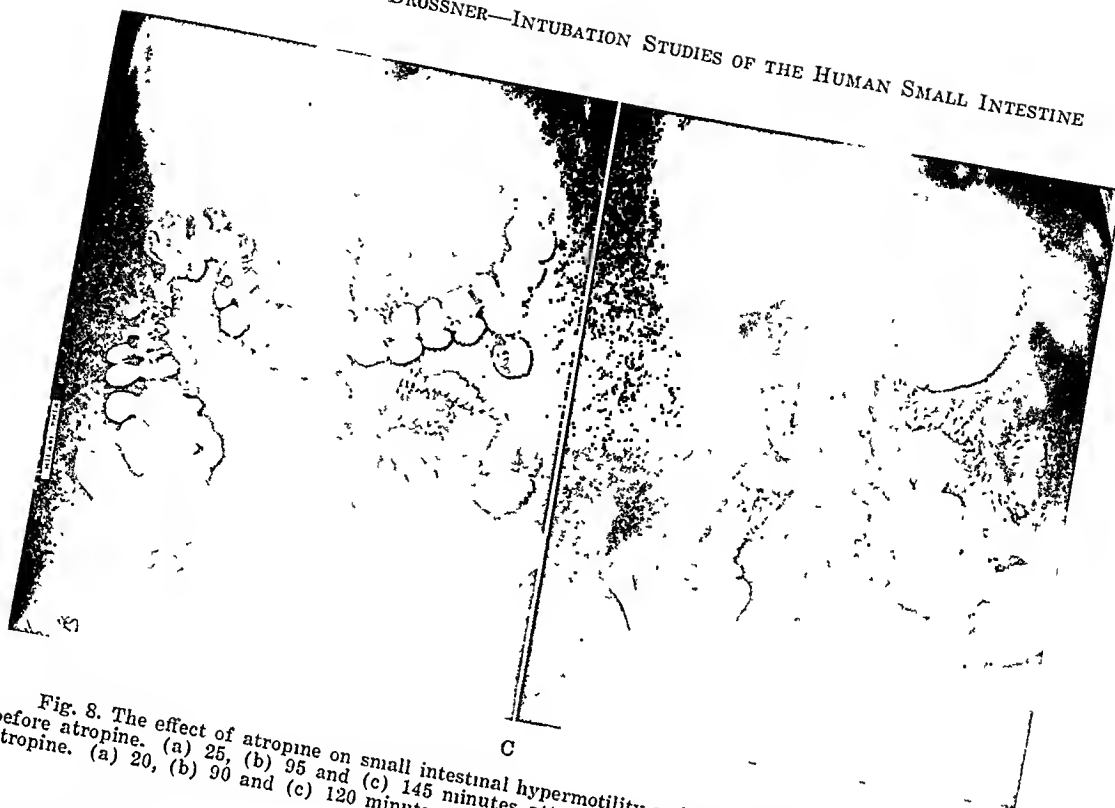


Fig. 8. The effect of atropine on small intestinal hypermotility and hypertonicity. Left hand column, before atropine. (a) 25, (b) 95 and (c) 145 minutes after a barium meal. Right hand column, after atropine. (a) 20, (b) 90 and (c) 120 minutes after a barium meal.

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XVIII. The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon*

By

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and
J. L. DROSSNER, M.D.‡

IN the present study the technique of intestinal intubation has been utilized to determine the effects on the human small intestine and colon of pitressin and amphetamine (benzedrine) sulphate. Similar studies of morphine (1) and of atropine (2) have been re-

ported from this clinic. The method of intestinal intubation makes possible the objective demonstration of drug effects on portions of the intact human intestinal tract hitherto inaccessible, and permits evaluation in man rather than in laboratory animals of the uses and limitations of drugs.

Methods and Subjects

The method of intestinal intubation as developed and carried out in this clinic (3) requires no further description here. It permits the introduction to any

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Fig. 1. The effect of pitressin on the duodenum of a normal subject. In this and the following figures the upper horizontal line represents the position of the writing lever when the balloon is empty, the base line its position when the balloon contains 40 cc. of air. Time in minutes.

portion of the intestinal tract of a balloon from which pressure changes may be recorded. A barium suspension introduced through the tube allows fluoroscopic observation of the bowel adjacent to the balloon. These two procedures complement each other, and with certain recognized limitations (1) constitute in our opinion a satisfactory method of study.

The subjects were without significant gastro-intestinal disease, except for one with ulcerative colitis in whom an ileostomy had been performed. In this subject the colon and terminal ileum were simultaneously intubated through the ileostomy opening. After suitable control observations the effects of pitressin or amphetamine were studied following hypodermic administration.

I. PITRESSIN

Effect on the Duodenum

The administration of 0.5 to 1.0 cc. of pitressin was followed in 2 to 6 minutes by a brief but marked spasm of the duodenum in 4 of 5 subjects. (Fig. 1). At this time fluoroscopic examination revealed a pronounced diminution in calibre of the duodenum which lasted 5 to 10 minutes and was accompanied by nausea and epigastric discomfort. Following this period of contraction relaxation of the duodenum occurred and persisted for 10 to 20 minutes; simultaneously duo-

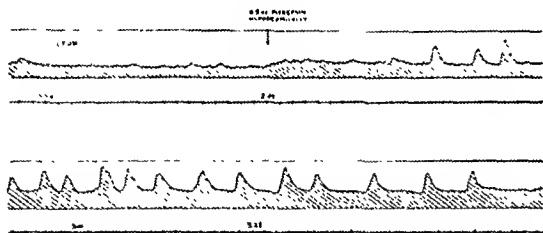


Fig. 2. The effect of pitressin on the ileum of a normal subject.

denal tone and peristalsis were reduced, and the subjective discomfort present during the period of contraction disappeared. The predominant effect of pitressin on the duodenum was, therefore, one of relaxation, since the initial period of contraction was relatively brief.

Effect on the Jejunum

The effect of pitressin on the jejunum was less definite than on other portions of the bowel. In none of 4 observations did 0.5 to 1.0 cc. of the drug produce striking results. Jejunal tone usually decreased slightly while peristalsis was increased. The small rhythmical waves consistently disappeared.

Effect on the Ileum

The administration of pitressin was followed by increased motor activity of the ileum in 12 observations

on 8 subjects. The evidence of this was of 5 types: (1) The pressure tracings often showed an increase in tone followed by the development of large peristaltic waves. (Fig. 2). (2) Fluoroscopic observation revealed hyperperistalsis, with rapid movement of barium from the terminal ileum into the cecum. This sometimes resulted from a peristaltic rush observed in the lower 18 inches of the ileum. The barium, in a continuous column before the administration of pitressin, was often divided into discrete segments, separated by narrow bands of contracted bowel. Peristaltic movement of the small bowel was visibly increased in most instances. (3) The tip of the tube, under the control conditions of our experiments, usually remained stationary once observations had begun. In several instances it advanced considerably during the



Fig. 3. Simultaneous tracings from the ileum and colon of a subject with an ileostomy for ulcerative colitis. The effect of pitressin.

action of pitressin. In one subject the forward advance of the tube had been stopped prior to giving pitressin by an acute kink of the ileum. After administration of the drug the tube traversed the angulation of the bowel without further delay. (4) In the subject with an ileostomy pitressin regularly increased the observable muscular activity of the exposed loop of ileum. (5) The amount and frequency of discharge of ileal contents in this subject were augmented after administration of the drug.

The activity of the ileum was modified by contractions of the colon produced by pitressin. Fig. 3 shows a record obtained by simultaneous intubation through an ileostomy of the terminal ileum and the colon. The first effect of the drug on the ileum was an increase in tone. During two spasmodic contractions of the colon the ileum was quiescent. This was evident both in the tracing and in the exposed bowel. As the colon relaxed increased ileal activity was resumed.

This reciprocal activity has also been observed fluoroscopically in normal individuals given pitressin. In one subject, with the tube in the terminal ileum, the outline of the gas-filled cecum was clearly visible. Following the administration of the drug rapid movement of barium through the terminal ileum occurred. The cecum and ascending colon dilated and remained quiescent during this period. The colon then contracted and the ileum became entirely inactive.



Fig. 4. The effect of pitressin on the ileum of a normal subject.

We have occasionally observed an effect on the ileum somewhat similar to that described in animals (4). (Fig. 4). Pitressin produced an initial increase in tone and an alteration in the character of the recorded waves. Rhythmical contractions disappeared, and large peristaltic waves occurred every 1 to 3 minutes. Be-

tween contractions the tone of the ileum was much below that in the control period but at the height of the contractions it far exceeded normal.

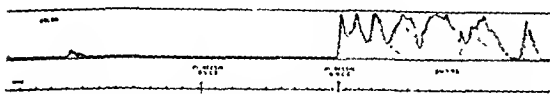


Fig. 5. The effect of pitressin on the colon of a normal subject.

Effect on the Colon

The effect on the colon consisted uniformly of an increase in muscular activity, amounting at times to intense spasm. Seven observations were made in 5 subjects. A representative tracing (Fig. 5) shows the abrupt onset of a series of contractions interrupted by brief periods of incomplete relaxation. Fluoroscopic observations made simultaneously were as follows:

pact, assumed a zeppelin-like shape and began a slow steady advance through the transverse colon and around the splenic flexure. After a momentary arrest coinciding with a period of relaxation indicated in the tracing, the barium column and tube progressed through the sigmoid colon to the rectum.

Fig. 6 shows in another subject the appearance of a segment of the descending colon before the administration of pitressin and during a contraction which followed its injection. The decrease in calibre and the loss of haustral markings of the colon and the increased compactness of the barium column are evidence of the intense contraction which was simultaneously recorded.

COMMENT

The action on the gastro-intestinal tract of posterior pituitary derivatives varies with the species tested and the conditions of the experiment. The literature on the subject up to 1929 is well reviewed

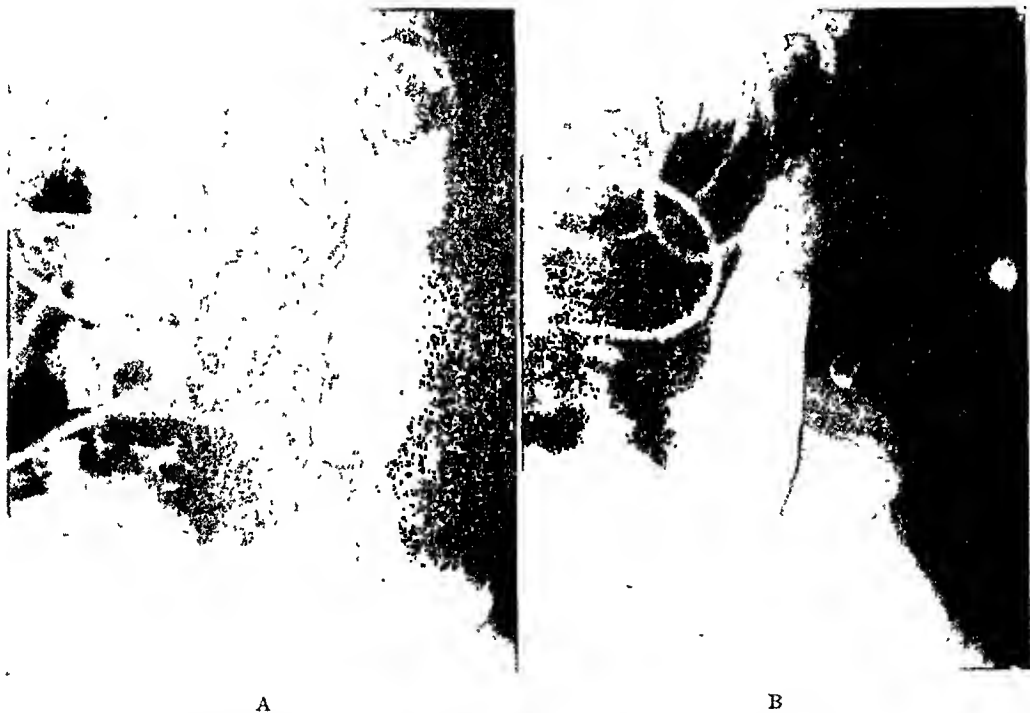


Fig. 6. Roentgenograms of a portion of the descending colon of a normal subject. (A) before pitressin, (B) after pitressin. Note that the tip of the tube and the balloon in (A) are at the splenic flexure. In (B) the tip of the tube has advanced and air has been forced from the balloon. Haustral markings are obliterated and the barium column is compact.

Barium outlined the entire ascending colon which prior to the administration of pitressin was of normal calibre and presented prominent haustral markings. During the control period no change was observed in the size of the balloon, which was situated in the ascending colon, or in the contour of the barium column. One-half cc. of pitressin was given without discernible effect in 10 minutes. After administration of an additional 0.5 cc. the outline of the ascending colon suddenly became smooth, the calibre decreased, the haustral markings were lost and air was forced from the balloon. At this point the first contraction was recorded on the tracing and the subject complained of "gas pains." The barium column became more com-

by Gruber and Robinson (4) and the rather confused status of the question is evident. Observations on the human published in the last decade, however, are in general agreement that augmentation of intestinal and colonic motor activity is produced by posterior pituitary preparations (5, 8). Their use in post-operative distention, and in eliminating gas from the bowel to permit proper roentgen visualization depends upon increased muscular contraction. Our observations have demonstrated a consistent increase in motor activity in the entire intestinal tract, with the two following qualifications: In the duodenum the prolonged after-relaxation which followed the initial contraction constituted the most characteristic effect of

pitressin. In the ileum the tone was sometimes decreased although peristaltic activity was augmented. However, the end result of the observed changes was invariably an increase in the forward propulsion of the intestinal contents.

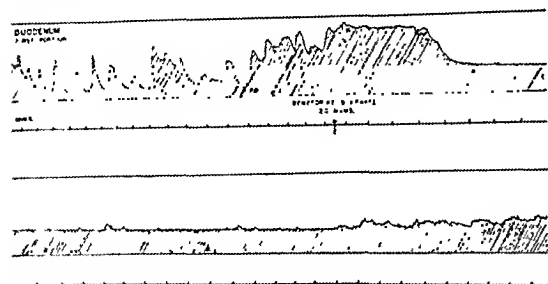


Fig. 7. The effect of amphetamine (benzedrine) sulphate on the duodenum of a normal subject.

II. AMPHETAMINE (BENZEDRINE) SULPHATE

Amphetamine (benzedrine) sulphate*, 0.015 to 0.020, was given to 18 subjects, a total of 21 observations being made on different portions of the normal intestinal tract. (Figs. 7, 8 and 9). Simultaneous tracings from the colon and ileum were obtained from the subject with an ileostomy. (Fig. 10). The results may be summarized as follows: In 12 experiments (57 per cent) no detectable changes were observed. In 9 observations (43 per cent) a reduction in tone and motor activity occurred. These changes were observed quite consistently in the ileum, but only irregularly in the duodenum, jejunum and colon. The effects qualitatively resembled those produced by atropine (2) but were as a rule of shorter duration and less regular in occurrence. This irregularity was not altogether due to individual susceptibility to the drug, since in one subject a striking effect was ob-

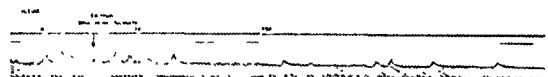


Fig. 8. The effect of amphetamine (benzedrine) sulphate on the ileum of a normal subject.

tained on 2 occasions and none on a third. In no case was the subject aware of the nature of the drug administered. In 2 instances unpleasant side effects consisted of nervousness and emotional instability. In several cases pleasant sensations of relaxation, increased mental acuity and mild euphoria were described.

COMMENT

Our observations are in general agreement with published data on the effects of amphetamine sulphate on the intact gastro-intestinal tract. Delay in final gastric emptying (9, 10), relaxation of the duodenal cap, small intestine and colon and decrease in small intestinal motility have been described (11, 12). Excised gut is stimulated by sufficiently high concentrations of the drug (13, 14). The use of amphetamine sulphate facilitates roentgen examination when abnormally high tone is a deterrent to proper visuali-

*Supplied through the courtesy of Smith, Kline & French Laboratories, Philadelphia.

zation. However, the clinical usefulness of the drug in various disease states of the gastro-intestinal tract is not a matter of general agreement (15). The inconstancy of its action which we have encountered constitutes a limitation, but when its effects are produced they are of potentially beneficial nature.

SUMMARY

The method of intestinal intubation has been employed in a study of the action of pitressin and of amphetamine (benzedrine) sulphate on the human small intestine and colon. Pitressin produced an increase in motor activity of the intestinal tract. Usually both tone and peristaltic activity were augmented; in some instances, however, the peristaltic increase was associated with a decrease in intestinal tone. After brief contraction of the duodenum prolonged after-relaxation was observed. In general the effects

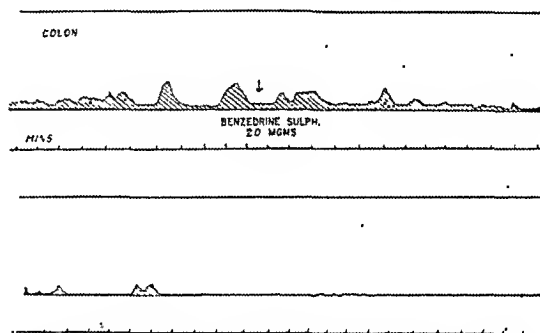


Fig. 9. The effect of amphetamine (benzedrine) sulphate on the colon of a normal subject.

of pitressin were more intense in the more distal portions of the tract. The activity in the ileum and colon bore a roughly reciprocal relationship in some instances.

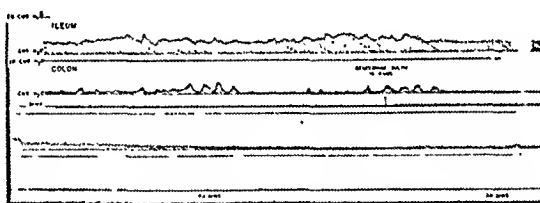


Fig. 10. Simultaneous tracings from the ileum and colon of a subject with an ileostomy for ulcerative colitis. The effect of amphetamine (benzedrine) sulphate.

Amphetamine (benzedrine) sulphate exerted a sympathomimetic effect on the small bowel and colon. Tone and peristaltic activity were decreased. The action of the drug was qualitatively consistent, though quantitatively it was less so, definite effects being produced in approximately one-half of the observations.

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DISCUSSION

DR. HEINRICH NECHELES (Chicago): We have studied two of the drugs used by Dr. Elsom but have obtained different results and I would like to ask him for a

possible explanation. The first drug was benzedrine which we tried on man and dogs. Contrary to the findings of Myerson we showed that it produced pylorospasm and apparently also spasm of the small intestine. Its effect on the colon was variable, relaxation and slight contraction occurring at different parts of the colon as well as in different tests. Our technique was different from that of Dr. Elsom, in that we used X-rays and barium.

We also studied the effect of atropine and of a new synthetic drug, known under the trade name of Trasentin (Diphenylacetyldiethylaminoethanol-Hydrochloride) in a number of patients with intestinal fistulas, gauging the effects of the drugs by the amount of fluid or the consistency of the feces voided through these fistulas. In the greater number of these patients atropine had none or very little effect, while the second drug terminated the discharge of watery fluid and produced, within a very short time, formed stools.

DR. KENDALL A. ELSOM (Philadelphia): It is very difficult, of course, to reconcile differences in the results when different methods have been used. I think that is one of the reasons for the great confusion that exists in the literature today.

I can't explain the differences between ourselves and Dr. Necheles. The doses of benzedrine we have used have been quite large, 15 and 20 milligrams given hypodermically. That may or may not explain the differences.

Observations on the Oral Administration of Citrated Blood in Man

I. The Effects on the Blood Urea Nitrogen

By

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IN the past few years numerous reports (1-11) have appeared indicating the frequency of blood urea nitrogen elevation following hematemesis or melena. Several factors have been invoked to explain this phenomenon. These comprise dehydration, starvation, shock, impairment of renal function, and absorption of products of decomposition of the blood liberated in the intestinal tract. We have confirmed the frequency of this change and have adduced evidence to show that it does not necessarily depend on starvation, dehydration, shock, or impairment of kidney function (12, 13).

Attempts to evaluate the importance of the relationship of the blood in the intestinal tract to the elevated blood urea nitrogen content following hematemesis have been made by several investigators. Sanguinetti (2) reported a maximum increase in the blood urea of 20 to 25 mg. % within two or three days in two persons given 1000 and 2000 cc. respectively of citrated pig's blood by stomach tube. Clausen (9) noted an increase in the blood urea of about 25 mg. % within eight hours after "infusing" 500 to 600 cc. of ox blood into the stomachs of two patients who had had a recent

hemorrhage. On the contrary, Sucic (4) obtained no increase in two patients in one and two days respectively, after administering 500 and 1000 cc. of calf's blood.

We have given citrated human blood to a group of fifteen individuals free of obvious renal disease (Table I). The blood used was that which had been stored in the blood bank of the Cincinnati General Hospital and had been discarded after a period of three weeks as too old to be used for transfusion purposes. It was previously tested for its urea content. It was kept at room temperature for an hour before it was allowed to flow by gravity into the fasting stomach through a Rehfuß tube, and into the jejunum or upper ileum and colon through a Miller-Abbott tube. About thirty minutes were required for the introduction. One thousand cubic centimeters were administered as a single dose to seven members of the group, while a total dosage of 2000 cc. was given to eight. A hypodermic injection consisting of codeine sulfate gr. 1 and atropine sulfate gr. 1/150 preceded the administration of the blood in order to prevent too rapid transit through the intestinal tract and thus permit of more adequate digestion and absorption.

No ill effects followed the administration of the blood. There was no nausea or vomiting. One individual had five loose movements containing bright

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From the Department of Internal Medicine, University of Cincinnati Medical School and the Gastric Laboratory, Cincinnati General Hospital.
*Justin A. Rollman Fellows in Medicine, 1938-1939, 1937-1938, respectively.

TABLE I
Clinical data on fifteen patients studied

Case No.	Hospital No.	Age	Sex	Diagnosis	B.P.	Fundi	Urinnlysis	Fasting B.U.N.
1	99066	29	M	Hematemesis—cause undetermined	106/60	Normal	Negative	9
2	101015	62	M	Hematemesis—cause undetermined	128/50	Normal	Negative	13
3	103691	19	M	Optic atrophy	120/70	Optic atrophy	Negative	12
4	98855	50	M	Duodenal ulcer (previous hematemesis)	150/60	Slight retinal angiosclerosis	Negative	13
5	101434	55	M	Duodenal ulcer (previous hematemesis)	130/73	Slight retinal angiosclerosis	Negative	10
6	Q1637	56	M	Superficial gastritis	132/90	Normal	Negative	10
7	98009	55	M	Atrophic gastritis	145/95	Normal	Negative	10
8	82152	34	M	Gastric ulcer	138/98	Normal	Negative	16
9	103825	49	M	Convalescent pellagra	150/96	Normal	Negative	21
10	54283	54	M	Atrophic gastritis	160/98	Slight retinal angiosclerosis	Negative	16
11	111986	49	M	Convalescent rheumatic fever	106/60	Normal	Negative	15
12	98689	41	M	Lung abscess	116/72	Normal	Negative	12
13	109726	27	M	Tuberculous cervical adenitis	112/74	Normal	Negative	14
14	115402	46	M	Convalescent lobar pneumonia	110/60	Normal	Negative	22
15	111542	23	F	Gonorrheal arthritis	98/60	Normal	Negative	10

blood twelve hours after receiving the blood into the jejunum. (This shows that, in the presence of intestinal hypermotility, bright blood may appear in the stools, though coming from high in the intestinal tract.)

After receiving the blood all of the patients were allowed to take food as desired, but, as a rule, did not eat until several hours afterwards. Determinations of the blood urea nitrogen were carried out before and at frequent intervals after the introduction of the blood. The determinations were made in duplicate by the aeration method of Van Slyke and Cullen (14). Specimens were obtained irrespective of meals because of the observation of MacKay and MacKay (15) that single meals containing a usual amount of protein have only a minor effect on the blood urea nitrogen. In a control group of nine subjects determinations made within two to three hours after meals were found to range between 9.6 and 21 mg. %.

Eight individuals received a total of 2000 cc. of citrated blood given at four-hour intervals in doses of 700, 700 and 600 cc. respectively (Fig. 1). In all eight a rise in the blood urea nitrogen occurred which exceeded the upper limits of normal (23 mg. %) (16). A maximum concentration of 24 to 57 mg. % was obtained within twenty-four hours of the first dose of blood. This was followed by a drop to normal on the second day in five and on the third day in the remaining three. These curves are similar to those obtained in patients with a single non-fatal hemorrhage from the stomach or duodenum and therefore emphasize the influence of the blood in the intestinal tract on the height of the blood urea nitrogen.

It is, of course, not known just how long there is actual bleeding in severe cases of hematemesis or melena. One wonders whether the patient usually has a single brisk hemorrhage lasting a short time or whether repeated bouts of bleeding occur at relatively short intervals. The resemblance of the curves shown in Fig. 1 to those seen clinically in cases of hematemesis or melena suggests that the actual bleeding is repeated.

It has been suggested that toxic products arising from the decomposition of the blood in the intestines may lead to impairment of kidney function (11), and thus account for elevation of the blood urea nitrogen. To exclude such a factor, determinations of renal function were carried out by the methods of Smith and associates (17) two days before and eighteen hours after the intragastric administration of 2000 cc. of blood. The eighteen-hour interval was selected because it represented a time period when the blood urea concentration was approaching its maximum (see Fig. 1). The results indicate that no significant change in renal function took place (Table II).

The effect on the blood urea nitrogen of varying the site at which blood was introduced was studied in seven individuals (Fig. 2). They were divided into

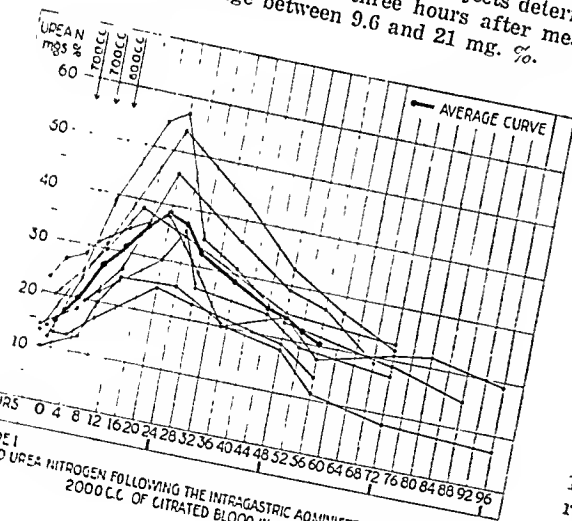


FIGURE 1
BLOOD UREA NITROGEN FOLLOWING THE INTRAGASTRIC ADMINISTRATION OF A TOTAL OF 2000 CC. OF CITRATED BLOOD IN EIGHT CASES

TABLE II

Renal function before and eighteen hours after beginning intragastric administration of 2000 cc. of blood

Case No.	Before Blood Administration				After Blood Administration			
	B U N. mg %	Clearances cc Per Minute			B U N. mg %	Clearances cc. Per Minute		
		Urea	Inulin	Phenol Red		Urea	Inulin	Phenol Red
1	12	88	104	357	26	94	114	333
2	13	38	68	221	51	38	70	262
3	11	81	103	292	35	81	127	351
4	14	72	93	270	54	70	110	298
5	13	47	74	242	37	38	71	270

groups of three, case No. 12 serving in each group. Each group received 1000 cc. of citrated blood as a single dose into (1) the stomach, (2) the jejunum or upper ileum, or (3) the colon. When the blood was given into the stomach, the urea nitrogen began to rise within two to four hours and reached a maximum

relationship of the digestion of the blood in the intestinal tract to the elevated blood urea nitrogen content.

The fact that no significant increase in the blood urea nitrogen followed introduction of blood into the colon coincides with our clinical experience in cases of hemorrhage from the colon and has proved of value in differentiating colonic from gastric or duodenal hemorrhage.

The effect on the blood urea nitrogen of varying the amount of blood introduced into the stomach was observed in one subject (Fig. 3). Following a control period of four days, during which he was on the regular ward diet, he was given 250 cc. of blood daily for eight days. With two exceptions a definite rise in the blood urea nitrogen was observed within twelve hours of the administration of each dose of blood and disappeared within twenty-four hours. Failure to obtain a rise after the first dose of blood may be explained by our waiting twenty-four instead of twelve hours before obtaining a blood sample. (This may also explain Sucic's failure to obtain a rise). This emphasizes the practical importance of carrying out urea determinations at intervals* not exceeding twelve hours when one suspects concealed hemorrhage from the stomach or duodenum. Failure to obtain an increase after the fifth dose of blood may have been due to a technical error.

*Determinations are best carried out at four-hour intervals, as we have seen the blood urea nitrogen double itself in this period following the administration of 1000 cc. of blood into the stomach.

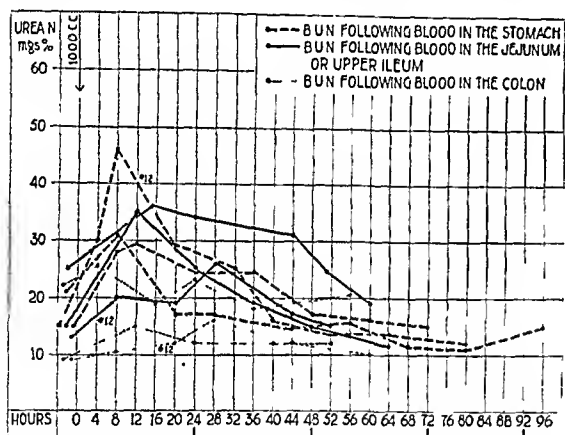


FIGURE 2
BLOOD UREA NITROGEN FOLLOWING ADMINISTRATION TO SEVEN PATIENTS OF 1000 C.C. OF CITRATED BLOOD INTO (1) THE STOMACH (2) JEJUNUM OR UPPER ILEUM AND (3) COLON

of 30 to 46 mg. % within twelve hours. This was followed by a return to normal within eighteen to thirty-eight hours.

When the blood was given into the jejunum or upper ileum, a maximum rise ranging from 26 to 36 mg. % was obtained within twelve to twenty-eight hours with a return to normal in twenty-eight to fifty-two hours. Following introduction of the blood into the colon no significant change in the blood urea nitrogen was observed during a period of fifty-two to sixty hours; the slight fluctuations which did occur may be considered to be within the normal range.

The fact that the maximum increase in the blood urea nitrogen was greater and occurred earlier when the blood was introduced into the stomach than when it was given into the jejunum or upper ileum may be explained by greater opportunity for digestion and absorption. Failure to obtain a rise when the blood was introduced into the colon may be explained by the virtual absence of digestion and absorption in this region. These observations again emphasize the re-

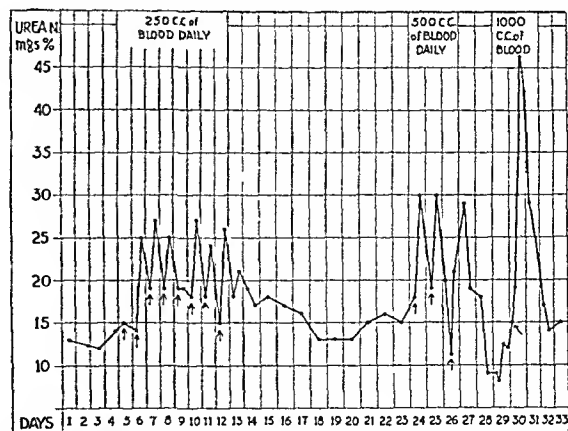


FIGURE 3
BLOOD UREA NITROGEN FOLLOWING INTRAGASTRIC ADMINISTRATION OF VARYING QUANTITIES OF CITRATED BLOOD IN ONE PATIENT

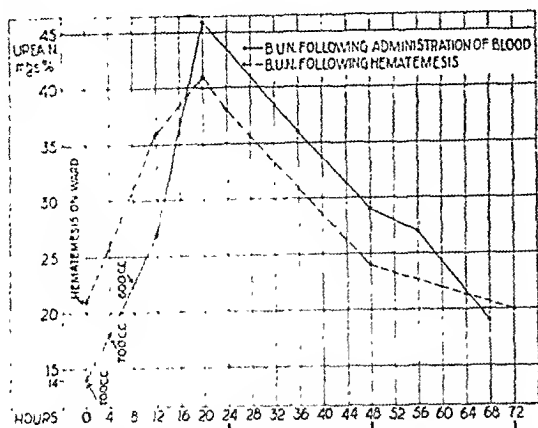


FIGURE 4
BLOOD UREA NITROGEN FOLLOWING HEMATEMESIS AS COMPARED WITH THAT FOLLOWING
INGESTION OF 2000 CC. OF CITRATED BLOOD IN THE SAME PATIENT

After a second control period of eleven days, 500 cc. of blood were administered on each of three successive days. Greater increases (of 11 to 18 mg. %) were obtained than those which followed the 250 cc. doses (6 to 11 mg. %). Four days after the last 500 cc. dose was given, a dose of 1000 cc. of blood was administered. An increase was noted within two hours and in twelve hours significantly exceeded that which followed the 500 cc. doses.

These observations show that the degree of blood urea nitrogen increase depends on the amount of blood administered at a given time. The time element may explain the disparity between the degree of anemia and the level of the blood urea nitrogen which is seen clinically in some cases of hematemesis. Thus, if a patient loses 2000 cc. of blood over a period of eight days, one might not expect the same degree of elevation of the blood urea nitrogen which would follow the sudden loss of this quantity of blood although comparable degrees of anemia develop.

Of much interest is a comparison in the same patients of curves of the blood urea nitrogen following massive hematemesis with those following the intragastric administration of 2000 cc. of blood (Figs. 4, 5 and 6). It is seen at once that the curves are strikingly similar, another substantiation of the importance of the alimentary factor in the elevation of the blood urea nitrogen following hematemesis. The quantity of 2000 cc. was arbitrarily chosen as, of course, we did not know just how much blood the patients had lost at the time of hematemesis. The quantity lost was evidently large as the number of red blood cells fell to between 1.0 and 1.7 millions per cubic millimeter.

In order to determine whether the elevation of the blood urea nitrogen following the administration of the blood was probably dependent on the protein content of the blood administered, determinations of blood urea nitrogen were made following the ingestion of large amounts of meat. It was planned to give a quantity of meat equivalent in protein content to the blood given, but this could not always be accomplished because of inability on the part of the subject to eat

the entire amount. The meat* was cooked for about two and a half to three hours and given in three doses at four-hour intervals. In Case 4 a total of 1.8 kg. of meat (equivalent to approximately 1700 cc. of blood) (19) was ingested. The blood urea nitrogen curve paralleled in a most striking way the curves obtained after administration of 2000 cc. of blood and after hematemesis (Fig. 7). In two other subjects given respectively 1.92 and 1.23 kg. of meat, appreciable rises in the blood urea nitrogen also occurred (Fig. 8).

These observations suggest that the elevation of the blood urea nitrogen following oral administration of blood may be attributed to the protein content of blood.

SUMMARY

The intragastric or intrajejunal administration in man of citrated human blood in single doses of 250 to 1000 cc. is followed by a significant rise in the blood urea nitrogen, which may begin within two to four hours, reaches a maximum within ten to twenty-eight hours, and usually returns to normal within forty-eight hours.

This increase in the blood urea nitrogen is proportional to the amount of blood administered. It also depends on the portion of the intestinal tract into

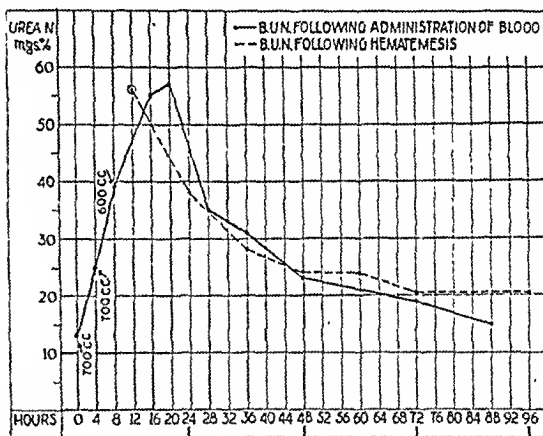


FIGURE 5

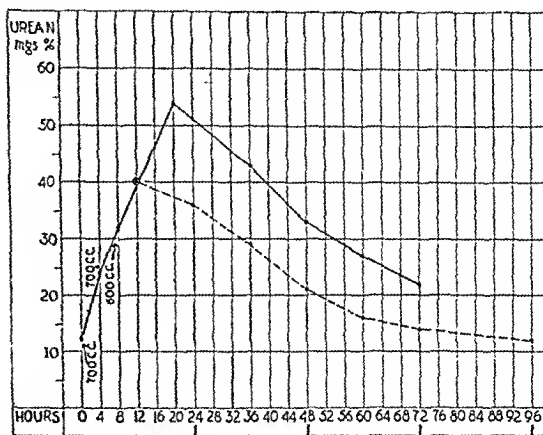


FIGURE 6

BLOOD UREA NITROGEN FOLLOWING HEMATEMESIS AS COMPARED WITH THAT FOLLOWING
INTRAGASTRIC ADMINISTRATION OF 2000 CC. OF CITRATED BLOOD IN THE SAME PATIENT

*Hind-quarter lean roundsteak = 20% protein (edible portion) (18).

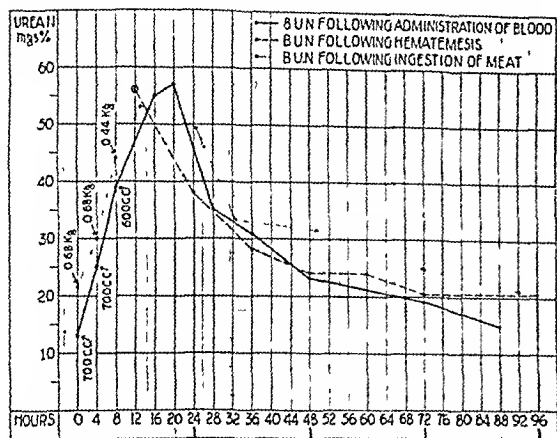


FIGURE 7
COMPARISON OF BLOOD UREA NITROGEN FOLLOWING (1) HEMATEMESIS (2) INTRAGASTRIC
ADMINISTRATION OF 2000 C.C. OF BLOOD AND (3) INGESTION OF 1.8 KILOGRAMS OF MEAT IN
THE SAME PATIENT (CASE 4)

which the blood is placed, occurring earlier and to a greater degree when the blood is introduced into the stomach than when it is introduced into the jejunum or upper ileum, and failing to occur when the blood is administered into the colon.

Curves of the blood urea nitrogen obtained in eight individuals after the intragastric administration of 2000 cc. of citrated human blood during an eight-hour period were quite similar to those previously obtained in twelve patients following a single severe, non-fatal hemorrhage from the stomach and duodenum.

In three patients there was a striking similarity between the blood urea nitrogen curves after hematemesis and those after the intragastric administration of 2000 cc. of blood, and in one instance after the ingestion of 1.8 kg. of lean meat.

The increase of blood urea nitrogen following intragastric administration of citrated human blood in man is not accompanied by impairment of kidney function.

CONCLUSION

The elevation of blood urea nitrogen which occurs after the introduction of blood into the stomach or upper intestinal tract is apparently dependent upon the digestion and absorption of the blood.

We wish to express our thanks to Dr. Paul Hoxworth, Director of the Red Cross Transfusion Service; to Doctors Benjamin Felson, Crawford Elsey and Jack Singer of the Department of Roentgenology, and to Misses Marjorie Hall and Dorothy McCrory of the Department of Dietetics for their cooperation in this study.

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DISCUSSION

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): One of the pressing problems confronting us and requiring solution sooner or later is the nature of the immediate prognosis following a massive hemorrhage. Is the hemorrhage for which the patient has been hurried into the hospital going to prove fatal or not? So far, we have no reliable criteria.

Doctor Schiff and his associates have confirmed what other investigators have previously demonstrated, namely, the importance of the factor of intestinal absorption of blood in relation to the elevation of the blood urea nitrogen, the prognostic significance of the latter within certain limits, and the passive role, if any, of the kidneys. Our own experiences are largely in accord with his. While there are exceptions to all rules, there is general agreement with the observation that the older the patient the greater the risk from hemorrhage, for various reasons. While Bennett's recent conclusions on the prognostic significance of blood volume studies following hemorrhage await confirmation, the results of such studies appear to be promising. Recent articles by Crohn and Snell on the subject of gastro-enteric hemorrhage are thought provoking and worthy of our close perusal.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): About four years ago one of my interns, Dr. Alfred Ingegno, made a study of the blood chemistry findings in a series of gastric hemorrhage cases at the Long Island College Hospital and reported his observations. He noted that in a large proportion of cases an azotemia occurred during

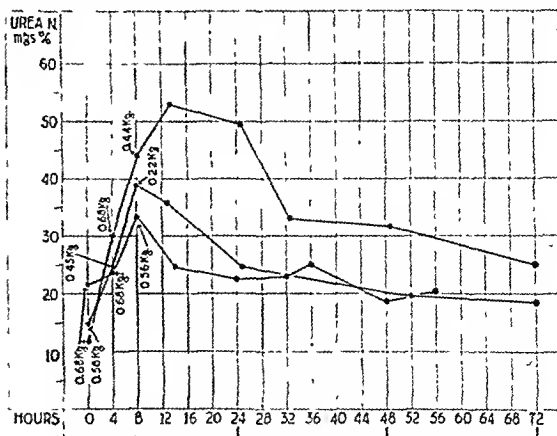


FIGURE 8
BLOOD UREA NITROGEN FOLLOWING INGESTION OF LEAN MEAT
(123 TO 192 KILOGRAMS)

the early stages following the hemorrhage and that the urea rapidly returned to normal when other findings indicated that bleeding had ceased. In the patients showing continued or recurrent bleeding the urea remained high, and Ingegno suggested that the presence of a continued azotemia might be used as an indication of continued bleeding. I am glad that the very important and ingenious study by Dr. Schiff and his associates tends to confirm these observations.

DR. A. C. IVY (Chicago): Mr. President, I should like to ask Dr. Schiff what diet these patients were on—for two reasons: In the first place, we have done some experiments in an attempt to answer the question: How much blood does a human being have to lose before a tarry stool becomes manifest? Our average figure is 60 cc. but I deliberately told the students performing this experiment to take a milk and cream diet. The figure given by the essayist was 120 cc. That is twice ours.

Of course, there may be a difference in the criteria regarding what color constitutes a "tarry" stool. The second point that I have in mind is that I observed, that the author's urea nitrogens were all in the lower range of normal, indicating to me that his patients were probably receiving a relatively low protein diet. On a high protein diet the urea values tend to be higher around thirty or forty.

However, I think the crucial point in the authors' experiment is that an equivalent amount of protein in the form of meat gave an equivalent rise in the blood urea nitrogen.

Another point—many of you have probably thought of this—if the patient has a chronic nephritis or if some of the factor of safety in the patient's kidney has been destroyed, then a loss of 500 cc. of blood would be more serious than in a patient who had a normal kidney and a normal factor of safety, because the loss of 500 cc. of blood would create an anoxemia which might lead to renal failure in the former patient, and probably not affect the latter patient, with the good kidney.

DR. BURRILL B. CROHN (New York): I am more or less called upon to discuss the paper, having just published on gastric hemorrhage and announced myself as not particularly convinced of the prognostic significance of urea estimations of the blood.

I have observed cases of hemorrhage from ulcer over a length of time, in one instance with hemoglobins very low hemoglobin readings. From a study of a series of cases of hemorrhage, I definitely have the opinion that the rise of urea is proportionate to the degree of shock, and that really significant rises of urea such as Meulengracht speaks of in his article, only occur directly after and as a result of shock, the mechanism being a prerenal azotemia.

It is true that I paid little attention to rises of urea up to 40 or 50 milligrams per hundred cc., which are the figures Dr. Schiff shows us today. Such figures are the result of concentrated proteins suddenly being shunted into the intestine. Two thousand cc. of blood weighs four and one-half pounds. That is quite a high protein diet (?) for a person in shock or hemorrhage to absorb without an elevation of urea.

Perhaps I may suggest to Dr. Schiff that there are two elements in the rise of urea following hemorrhage. One is the factor of rapid absorption of a huge amount of concentrated protein suddenly thrown into the alimentary

tract, and the other, which is the real factor, the prerenal azotemia as a result of shock, and the fall of the blood pressure. The element of shock is the real factor, and the significant rises of urea occur only when the hemorrhage is acute, precipitate, and large in amount, and the rises of urea are proportionate to the degree of shock rather than degree of loss of blood.

As for saying that the renal tests show no difference in kidney function, I don't think that the modern kidney tests are sufficiently delicate to really indicate an imbalance in the kidney function.

In pyloric stenosis you know and we know that definite kidney changes take place, calcification and degeneration, and there is a definite clinical picture associated with pyloric stenosis and yet no tests show any imbalance or changes of kidney function even though there are definite organic changes in the kidney.

DR. LEON SCHIFF (Cincinnati, O.): We are very grateful to the members who have been kind enough to discuss this work. We have been impressed with the prognostic value of the blood urea nitrogen in our clinical studies. In fifty-three cases which we are reporting elsewhere,* five had a blood urea nitrogen content of over 100 milligrams per cent, and four of these died. The fifth had chronic nephritis with renal insufficiency which probably influenced the degree of his elevation. It is interesting that we found no constant relationship between the age of the patients and the degree of elevation of the blood urea nitrogen. We should like to give due credit to Dr. Ingegno, who, in a brief paper in 1935 stressed the occurrence of this phenomenon and its prognostic significance.

In reviewing the literature on blood urea studies it is frequently difficult to determine whether the author is dealing with blood urea or with blood urea nitrogen. The former is normally 2.14 times the latter. Our figures deal only with the blood urea nitrogen which, in our hands, has been found to normally vary between 9 and 21 milligrams per cent. We believe, therefore, that a concentration of 30 milligrams per cent or over represents a significant increase.

These patients, Dr. Ivy, were on a regular ward diet, with the usual amount of protein. We have occasionally obtained tarry stools following the oral administration of 75 cc. of blood, but, in order to uniformly obtain tarry stools, we have had to give 100 to 150 cc. of blood.

As Dr. Crohn mentioned, one occasionally finds a low blood urea nitrogen in the presence of a very low hemoglobin concentration. We believe that the rate at which the hemorrhage occurs explains this disparity. Thus, for example, if the hemorrhage occurs quickly, one may expect a rise in the blood urea nitrogen, but if it occurs slowly, one may not expect this rise although an equivalent amount of blood may be lost.

It is true that shock will, through its secondary effect on renal function, elevate the blood urea nitrogen. We have shown, however, in the study to which I alluded, that shock is not an essential factor in the elevation of the blood urea nitrogen which follows hematemesis. It is true, nevertheless, that the highest blood urea nitrogen values are more commonly seen in individuals with shock than in individuals without this manifestation.

Dehydration and starvation may likewise play a role in the elevation of the blood urea nitrogen, but we have satisfied ourselves that their role is not essential as we have seen the blood urea nitrogen rise in five or six hospital patients who were on a Meulengracht diet with an abundance of fluids at the time of a second hemorrhage.

*Archives of Internal Medicine (in press).

The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester, and Phospho-lipid Tests in Diseases of the Liver*

I. The Results of the Tests

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FOR many years investigators have attempted to find a test which would give a good index of the condition of the liver in the human patient. It is now generally accepted that no *single* laboratory test has been devised which will serve this purpose.

In the last five years on the second and fourth (Harvard) Medical Services at the Boston City Hospital about 300 consecutive cases of jaundice have been intensively studied and various liver function tests used.

This communication deals with the results of a special study in the past year of 66 cases of hepatic disease, nearly all of which exhibited jaundice. The tests used were total cholesterol, ester cholesterol per cent, phospho-lipids, hippuric acid excretion, icteric index, urobilinogen and bromsulphalein excretion.

Our object was to obtain, if possible, a better idea of the condition of the liver and to compare the different tests, to see how far they could be used in diagnosis and prognosis.

We know that the liver functions are constantly changing during an attack of jaundice from the onset to the height of the jaundice and during convalescence, and, therefore, stress has been placed on the frequent repetition of the laboratory tests during the course of the illness and in some instances for many months after the attack had subsided. Although the series is not a large one we have gained in this way much additional information both from the standpoint of the individual patient and also as to prognostic significance of the various tests. Though the advantages of *serial liver function tests* are often mentioned in the literature, they seem to be more often mentioned than used. In our series where both hippuric acid and cholesterol ester tests were normal in mild and convalescent cases, the tests were not apt to be repeated.

The series is also interesting because it includes twenty patients with chronic cirrhosis. This condition must often be considered in the differential diagnosis of painless jaundice but it has received less attention from a laboratory standpoint than the cases of severe acute liver disease, in which the results are much more striking.

The following tests were chosen because they are suitable for use in a jaundiced patient, and because

there has been considerable discussion and disagreement about their value both in differential diagnosis and prognosis. Some tests such as the bilirubin excretion or bromsulphalein tests were considered unsuitable or unnecessary in the presence of jaundice. The modified bromsulphalein test was only used to determine residual liver damage after the jaundice was gone.

METHODS

The hippuric acid excretion was studied by the gravimetric method of Quick (1, 2) because the precipitate in addition to hippuric acid yields unknown, but very small amounts of unconjugated benzoic acid and glucuronic acid which might give erroneous acidity values by the titration method. The absence of characteristic hippuric acid crystals required fractional evaporation until these could be identified. This test is based on the theory that sodium benzoate is conjugated with the glycine of the body by the liver and is excreted as hippuric acid. An excretion of 2.5 to 3 grams was considered normal. This test was only considered significant where we had approximately normal renal function as measured by analysis of the urine, the non-protein nitrogen of the blood and a concentration test of the urine.

The Rosenthal (3) bromsulphalein test was modified to include the study of blood samples withdrawn at 2, 5 and 15 minute intervals after the injection of 2 mgm. of the dye per kilo of body weight.

This was found to be a more delicate test than the one-half hour residue in a group of non jaundiced patients after recovery from acute hepatitis.

The normal two-minute sample may show as much as 80% retention in the older age group, while younger persons may have as high as 30-40%. The five-minute sample rarely contained more than 15%, while the 15-minute sample normally might show as much as 5% retention.

The phospho-lipid determination includes the extraction of plasma lipid by the method of Bloor (4). A portion of the extract which was evaporated to dryness, was digested* with sulfuric acid and potassium persulfate, and the phosphate determined using aminonaphthol sulfonic acid. The normal range is 3-9 mgm. %.

Total lipids were determined in several cases but

*From the Second and Fourth (Harvard) Medical Services and the Surgical Research Laboratory of the Boston City Hospital.
Read at the forty-second annual meeting of the American Gastro-Enterological Association, Atlantic City, May 1, 1933.

*Unpublished data of C. H. Fiske and Y. Subbarow of the Department of Biochemistry, Harvard University.

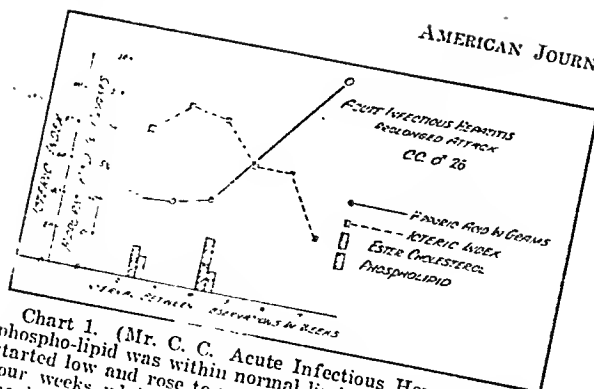


Chart 1. (Mr. C. C. Acute Infectious Hepatitis). The phospho-lipid was within normal limits; the ester per cent started low and rose to normal fairly early, at the end of four weeks while patient was still deeply jaundiced and the index 100; the hippuric acid excretion remained low for four to six weeks and became normal only at the end of seven weeks, while the patient was still moderately jaundiced.

were found to rise and fall with the phospho-lipid and total cholesterol, giving no added information, so were discontinued.

The total, free and ester cholesterol were determined by Smith and Marble's (5) modification of Bloor and Knudson's method (6) which saponifies the esters and, therefore, yields more uniform results. In the original Bloor and Knudson method where saponification is not used, the values may be 10% or more higher than with the Smith and Marble modification. We have considered an ester percentage of 60%-70% as normal. The blood must not be hemolyzed for the cholesterol tests, because the red cells contain only free cholesterol which, if liberated by hemolysis, gives an abnormally high value.

Urobilinogen was measured in the urine by the method of Wallace and Diamond (7). The bleeding time was measured by the Ivy method (8). There are some practical limitations or disadvantages for each type of test; for example, in the tests which require blood chemistry such as the phospho-lipids, total cholesterol, and cholesterol esters, vein punctures must be repeated for serial tests and

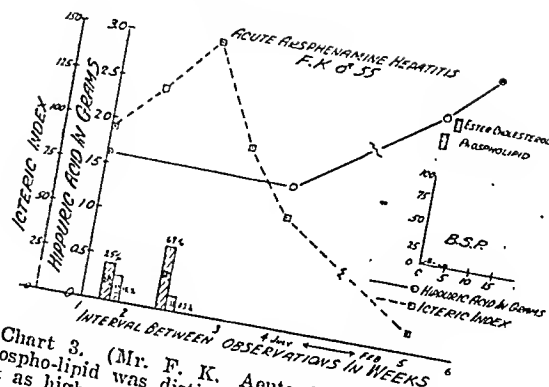


Chart 3. (Mr. F. K. Acute Toxic Hepatitis). The phospho-lipid was distinctly high at first (19.2) though not as high as most of our obstructive cases. The ester per cent started low and rose early to normal at the end of a week and a half while the biliary index was 100 to 125. The hippuric acid excretion remained low for over a month, but was found to be normal at the end of five and six months. A B.S.P.* test done seven or eight months after the attack of jaundice showed no retention.

it is desirable to keep the veins in good condition for treatment with glucose solution especially in the sicker patients who cannot take glucose by mouth. The urgent need of using the veins passes (for the time at least) when the jaundice is over, so the objection to a method requiring puncture of a vein, does not apply to the bromsulphalein method as we used it, to show residual damage. The cholesterol analysis is also somewhat elaborate and requires more time and experience than the other tests.

The dose of benzoic acid given for the hippuric acid excretion test may be mildly distasteful or very rarely cause vomiting, the latter only occurred once in these 66 cases. Quick has proposed a method of intravenous injection of hippuric acid to avoid this difficulty. Our impression is that it will be rarely needed except in very sick patients or at once after operation.

Normal renal function has seemed to us very important. The non-protein nitrogen has always been determined; also the ability to concentrate the urine. We felt that the hippuric test could not be relied on

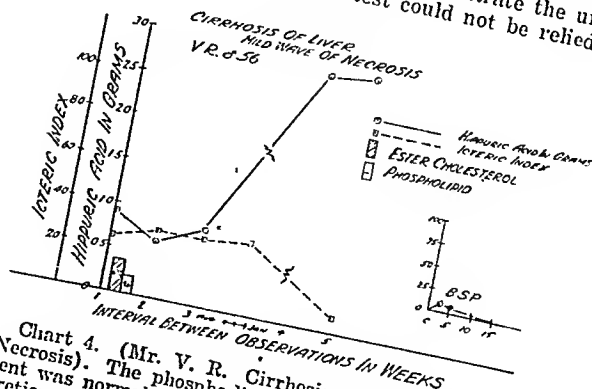


Chart 4. (Mr. V. R. Cirrhosis with a mild wave of Necrosis). The phospho-lipid was normal; the ester per cent was normal even at the start; the hippuric acid excretion was low for about a month and was normal at the end of four months later. The low hippuric acid excretion bore little relation to the jaundice which was mild. At the end of five months when the jaundice was gone, a B.S.P.* test was normal.

*B.S.P. = bromsulphalein.

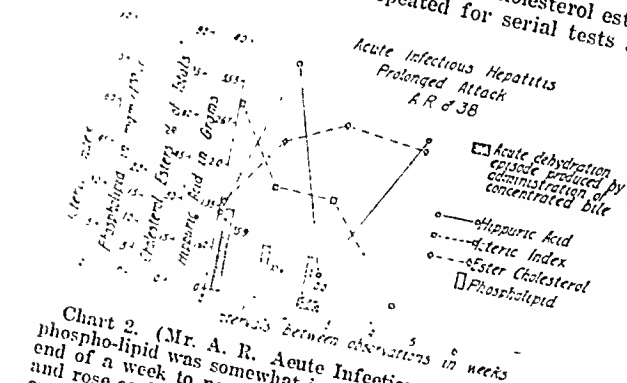


Chart 2. (Mr. A. R. Acute Infectious Hepatitis). The phospho-lipid was somewhat increased, but dropped at the end of a week to normal. The ester per cent started low and rose early to normal. The hippuric acid excretion started low, became normal at the end of a week and a half; later during an attack of acute dehydration due to profuse acute vomiting and diarrhea, the hippuric acid excretion fell to a low point, and then recovered to normal. This episode illustrates the striking effect of dehydration and poor kidney function on the hippuric acid excretion test.

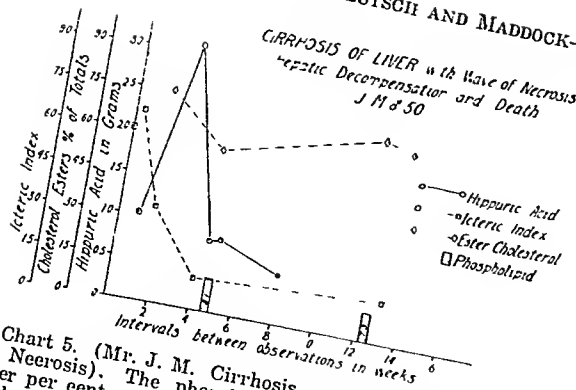


Chart 5. (Mr. J. M. Cirrhosis—a fatal case with wave of Necrosis). The phospho-lipid remained normal; the ester per cent remained normal throughout 14 weeks, up to the time of the patient's death, showing its lack of value in prognosis. The hippuric acid excretion was first low, then normal during a period of vigorous regeneration of the liver, then became low and remained so even though the jaundice was gone. (The hippuric acid excretion tests had to be discontinued after the eighth week as the patient became irrational and incontinent).

when nephritis or obvious dehydration was present or in so-called hepato-renal cases, a complex and rather poorly defined group of clinical disorders in which liver injury or infection, is associated with renal lesions or dysfunction.

A period of marked dehydration such as is seen in Case 13, Chart 2, will interfere with renal function and the use of this test. We have wished to test the renal circulation in some of our cases to see if it had an effect in lowering the hippuric acid excretion, but know of no simple way to do this and have noted that a moderate degree of circulatory failure such as was occasionally found, has not seemed to interfere with the excretion of hippuric acid.

The collection of the urine at the end of four hours

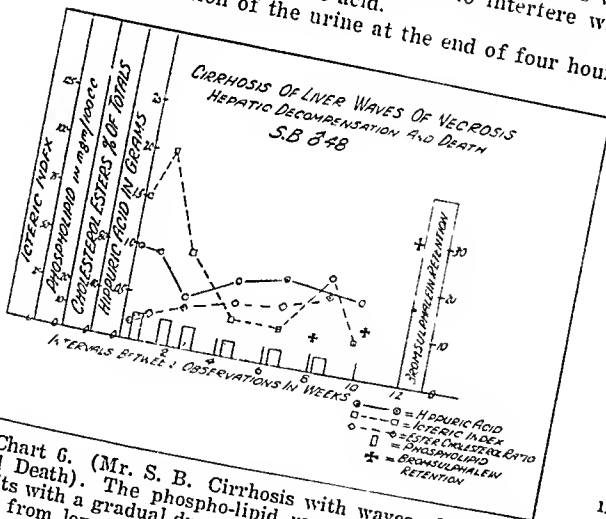


Chart 6. (Mr. S. B. Cirrhosis with waves of Necrosis limits with a gradual drop. The ester per cent rose gradually from low to normal at the end of two months, just before his death, showing its entire lack of prognostic value in this case. The hippuric acid excretion was always low, one gram or less, and the hippuric acid excretion and compensation. B.S.P. tests in the last two weeks of life when the hippuric acid excretion was low showed progressive retention and a clear picture of the bad prognosis.

B.S.P. = bromsulphalein.

required simple cooperation on the part of the patient and nurse. In a sick patient who is incontinent, the test fails.

In Table I complete data are presented in each of the various types of liver disease. The tables indicate the dates of tests; the duration of the jaundice before entrance to the hospital, the Icteric index, the hippuric acid excretion in the urine in grams, the phospholipids and total cholesterol in the blood in milligrams, and the percentage of cholesterol ester. The urobilinogen figures represent the dilution in which the test was positive; e.g., 64 means positive in a dilution of 1 to 64. The Ivy bleeding time was noted in seconds and the bromsulphalein test by the method described, in per cent of retention at 2, 5 and 15 minutes. Table II gives a summary of the significant changes in the entire series showing the per cent of cases in which the tests were low, normal, increased or went from low to normal. The figures under the titles of the different tests show what we have considered normal.

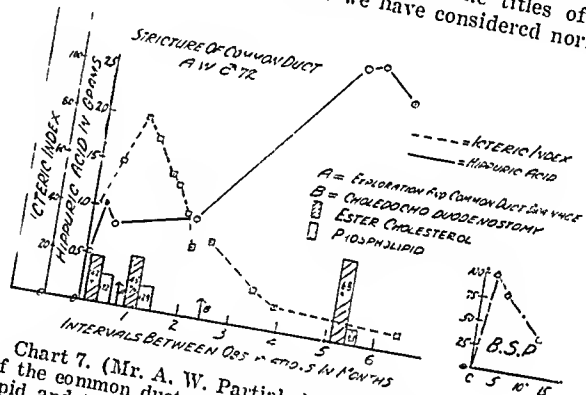


Chart 7. (Mr. A. W. Partial obstruction due to stricture of the common duct, with two operations). The phospholipid and total cholesterol were rather high at the outset due to partial obstruction and both became normal after the first operation, drainage of the common duct. The ester per cent was low at the outset, remained low after the first drainage operation and then finally became normal after the second (short circuit) operation. A biopsy of the liver showed biliary cirrhosis. The hippuric acid excretion followed a similar course, but at a lower level and reached normal in five months. Tests were omitted on account of severe illness during the third and fourth months. The B.S.P. test at the end of six months showed 40% retention. A later test, not shown on the chart, at the end of eight months showed no retention. The B.S.P. tests showed the very slow recovery from the liver damage and were positive at a period when all other tests were normal.

Results—In general the results of the various tests were as follows:

The lipid-phosphorus values were for the most part normal with the notable exception that in the cases of obstructive jaundice almost 90% were markedly increased, i.e. 13 to 33 mg. (Normal 8-9 mg.). In a few of the cases of acute infectious or toxic hepatitis there was also an increase, showing 14-16 mg. in the infectious cases (catarrhal jaundice) and 19-27 mg. in the toxic cases (arsenic, chloroform thyroid). One case of acute yellow atrophy of the liver not included in the series showed a phospho-lipid value of 3.0 mg.

The total cholesterol behaved very similarly to the lipid-phosphorus and was increased in approximately the same cases of obstruction, showing variations be-

TABLE I

[illegible]

TABLE I (CONTINUED)

CHRONIC CIRRHOSES (Continued)											
No	Date	Days of Jaundice	Index	Hippuric	Phos Lipids	Cholesterol		Urob	Bromsulph Retention	2' 5' 16'	Comment
						Total	Ester %				
24	3-25-39 4-10 4-13 4-24	3 wks.	50 35 30 15	2 03 1 51		201 164	41 67	266 256 0 4			Portal with acute necrosis Admitted to surgical service as obstructive Lues
26	4-18-39	0	8			276	76	4-18	90 30 6		Portal, 6 years ago jaundice explored, biopsy, recurrent ascites Takata +++ AG ratio 1.95-
26	4 4-39	90	200		11 0	129	26				
27	7-29-38 8-11 8-30 10-25 11-2	14	70 15 15 10 15	1 07 3 06 0 78 0 82 0 58	8 1 7 3	220 181 224 191	55 57 63 60	128 64 32 61	$\frac{1}{2}$ hour = 30		Portal, variable course Recurrent ascites
28	9-26-38 10-13 10-25	21	90 85 25	0 31 1 37	6 7	176 143	54 71	64 64 64	$\frac{1}{2}$ hour = 100		Portal, jaundice subsided Ascites developed Cholema death
29	10 4-38 10-15 10-31	0	13 10	0 80 1 85 1 71	6	114	66	266 32 32	$\frac{1}{2}$ hour = 0		Portal—Course of tests helped to rule out cancer
30	9-27-38 9-29 10-27 12-28 1-13-39 6-1	7	50 38 5 15 5	1 74 1 61 1 93 2 57 2 21 2 53	9 0 7 6	189 116	60 63	32 0 0 0 16			Portal—Recurrent D.T.'s Liver damage variable Korsakoff's psychosis Marked anemia
31	10-26-38 11-2 11-12 11-25 12-12	7 6	60 100 50 20 50	0 95 0 91 0 51 0 76 0 87	11 7 11 3 9 0 6 7 6 7	193 163 167 141 140	14 22 36 42 62	8 32 16 128 32	9 4 2 (12-1-38) (12-10-38) 10 (12-31-38) 30		Portal—Progressive downhill course Death P.M.
32	11-29-38	0	16-20	0 93		112	11	128			Portal—Long alcoholism Palpable liver Died broncho pneumonia
33	12-6-38	1 yr	75	1 04	9 2	118	50	256			Portal—Long alcoholism Deep jaundice purpura Transferred to another hospital
34	2-28-39 3-2	6 mos	60 30 20 15	1 02 1 81				0 8 64 S			Portal or subacute toxic recurrent jaundice Bleeding tendency
35	5 9-39 5-16	0	20 7	1 00 1 65	15 5	218	62	164			Mild cirrhosis and diabetes with
36	1-26-39 2-18 2-28 3 15	6	100+ 100+ 100	0 79 0 96 0 25	9 4 9 5	120 142	43 42				stone, biopsy cirrhosis died 6 weeks later Cholema
37	4-20-39 4-27	1	4	1 60 1 40		100 98	70 55	32			Fatty degeneration of liver Lues arsenamine Terminal miliary tuberculosis Death
38	4-17-39 5-18 6-1	1	55 42	2 39 3 29	9 7 7 8	144 184	46 50	128 74 16			Cirrhosis probable Cancer not entirely ruled out
TUMORS											
39	6-1-38 1-27-39 2 4 5 5	0	25 14 15	0 66 0 80 1 41 (too sick)	6 6 6 9	144 102	61 44	64 32 8 16			Hemangio blastoma diagnosis of cirrhosis at operation 4 years previous Biopsy of neck gland hemangio bl stoma A-G ratio 1.82-1.97
40	10-13-38	0	5	1 47	9 6	234	65				Sarcoma of eye removed 3 years before Nodular liver No jaundice
41	2 17-39	0		2 91							Leukemoid blood picture marked anemia Large rubbery liver with good function Comfortable but weak
42	11-22-38	0	10 4	2 20	8 9	160	64				Sarcoid of lungs liver spleen and skin (biopsy) No jaundice Serological lues
HEMOLYTIC JAUNDICE											
43	6-6-39 6-7 6-9 6 10 6-13	0	150 95 25	0 0 1 33 2 57	6 0 5 7	103 146	31 55				Hemolytic jaundice Sulphanilamide Toxic hepatitis
44	5-9-39 6-10 5-27	1 yr	70 35 50 20	2 60	6 9 5 6	110 135	70 65	16		30 5 2	Typical hemolytic jaundice with moderate icterus and normal liver function Reticulocytes 67% to 63% Total lipid 431
45	5-16-39 5-25 5-31	2	50 10	3 31 3 84	6 9	178	61	8		3 2 0	Acute hemolytic anemia, normal liver function Two transfusions Reticulocytes 24%-16% Total lipid 50

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TABLE I (CONTINUED)

OBSTRUCTIVE JAUNDICE												
No.	Date	Days of Jaundice	Index	Hippuric	Phos. Lipids	Cholesterol		Urob.	Bromsulph. Retention	Comment		
						Total	Ester %		2' 6' 15'			
46	6-6-39 6-13	77	170 160	Very low Very low	32.1	463	11					Cancer common duct and liver. Desired operation. Very poor risk. Death—no bleeding, no peritonitis.
47	8-10-38 8-19 8-29 10-22 1-26-39 2-2-39 2-2-39	14	40 50 60 35 17 0	0.50 1.02 .88 1.01 2.88 2.90	17.2 12.9	287 236	42 45	32 32 32 8	(3-27-39) 100 80 40 (4-22-39) 20 0 0			Benign stricture com. duct. 2 operations, drainage of gall bladder and short circuit. Biopsy biliary cirrhosis. Recovery.
48	9-2-38	7	60-75	1.97	9.7	210	68	16	4-2			Cancer head of pancreas. Operation, death.
49	8-31-38	11	105	2.75	33.6	169	53					Cancer head of pancreas. Operation, death (cholelith?).
50	10-11-38	14	60	0.52	22.7	478	17					Cancer liver, marked obstruction of ducts, secondary to cancer of stomach. Semi-omn. Died soon after admission. P.M.
51	3-22-39 3-27 4-6	90	80 100 100	1.82 1.35	20	213 268 293	33 35 48	0 0 0				Cancer head of pancreas. Refused operation 3 months before. Operation. Relief.
52	7-27-38	2	18-15	2.48	20.8	511	71	8				Partial obstruction from adhesion about common duct. Operation 9-10-38.
53	7-20-38	73	45-80	0.70	14.4	254	55	0				Cancer of liver and ducts secondary to cancer of rectum. Rapid downhill course, deep jaundice. Liver nodular. Death P.M.
54	1-20-39 1-30 1-31 2-20	1	100+ 150 200 25	1.07 1.67	10.1			0				Operation. Stones in common duct.
55	4-6-39 4-13 4-27 5-3	7	40-20	1.29 2.28	24	193 335	56 50	0 4				Gall bladder, common duct stone. Operation. Diabetes mellitus. Slow recovery.
56	4-21-39 5-3	7	40 60	0.5 1.77	13.2 11.5	253 241	68 65	64-8				Cancer of head of pancreas. Progressive, obstructive jaundice. Left hospital against advice.
GALL BLADDER DISEASE (WITHOUT KNOWN OBSTRUCTION)												
57	2-21-38 2-1-39 2-10 3-22-39 3-25 4-5 4-13 4-27 5-23	3	18 12 18 75-70 110-70 10	1.54 2.90 2.45 1.63 2.24 2.41 1.10 1.81 2.18 1.40	11.6	284	67	128 30 16 8 8 8 16 256				First attack of mild jaundice rapid recovery. Normal liver function 5 mos. later. Graham +.
58	12-23-38	6 mos. Intermittent	60-10	3.34 3.01	8.1	166	67	64-32	30 7 2			Gall stones. Pancreatitis hepatitis. Bleeding tendency. Vitamin K used. Operation 5-10-39.
59	11-26-38 3-30-39 4-2 11-2-38	14	12-40 7 7 10	0.71 1.73 1.10	7.1	288 133 186	56 62 60	16 64 16 32 64				Recurrent attacks of jaundice. Graham +. Poor surgical risk.
60	11-10 10-8-38	Intermittently 6 yrs.	25-15	1.48	8.3	186	61	32	30 20 0			Gall stones. Giardiasis, cholecystectomy. Common duct empty.
61	5-2-39 5-16 6-6	4	80-40 60-18	3.23	13.4 9.5	204 234 237	47 53 76	128 61				Large solitary gall stone. Rapid recovery. Refused operation.
62	4-6-39 4-15 4-20 5-8	6 wks.	90 100+ 60 25	1.40 0.55 1.41 2.52	85 63 53 11.3	125 93 100 64 61	64 61	0 257 64 128				2 previous G. B. operations. Poor risk. Died coronary thrombosis.
63	4-7-39 4-15 5-8	1 day	40-15 8 20-80 25 20	1.39 2.46 3.68 1.05 1.80	14.4	170 157 63 69	64 63 69	64 128-16				Gall bladder, broncho-pneumonia. Rapid convalescence.
64	6-1-39 6-12 6-19		Very low			178 141	43 48	64 128 64				Pancreatitis with walled off abscess in epigastrium. Operation.
65												Graham + after jaundice gone. Large solitary stone. Operation. Rapid recovery.
66												Cholangitis ? pathologic gall bladder. Sulphanilamide used. Septic fever 4 weeks. Operation.

253-478 mg. per 100 cc. (normal 150-220 mg.) was normal or only slightly decreased in the chronic cases, i.e. cirrhosis, and gall bladder without obstruction of the

period of observation

tween 253-478 mg. per 100 cc. (normal 150-220 mg.) and it was normal or only slightly decreased in the other chronic cases, i.e. cirrhosis, and gall bladder disease without obstruction of the common duct. In a few of the cases of acute hepatitis the values were moderately low during some period of the illness. The cholesterol ester percentage (normal 60-70%) was low in about 68% of the cases of acute hepatitis. One-half of these returned to normal upon improvement of the patient, the rest remained low during the

period of observation. The milder cases, 32 per cent, were always normal. There were two deaths in this group, both of which had a low ester percentage (34 per cent and 10 per cent). In the chronic cirrhoses, the percentage of ester cholesterol was low in 45 per cent of the cases. One-half of these returned to normal and the other half remained low. Almost twice as many chronic cases as acute were always normal. In five out of eight deaths in this group the percentage of ester was normal, or

had improved from low to normal. In the other three deaths the ester values remained low.

In the gall bladder cases without known obstruction, the normal and low percentages were about equally divided and only about 1/10 remained low. Perhaps this would have been a still smaller number if the patients had been held and observed longer.

In the tumors, all the ester cholesterol percentages were normal.

The small group of cases of obstructive jaundice, which was included for comparison, was composed of seriously ill individuals. Seven of the eleven cases had neoplasms, four of the head of the pancreas, two of the liver and ducts and one of the common duct. Five of these patients died. The ester cholesterol percentage was low in three cases (11%, 17% and 23%); slightly below normal in two cases (53% and 55%) normal in one case 68% and in one case was low and increased from 33% to 48% following choledochoduodenostomy. In one case of benign stricture of the common duct the percentage was normal (71%) and in another rose from low to normal (42% and 68%) after a short circuit operation. In two cases of common duct stone the values were just below normal (56% to 50%).

Hippuric acid excretion was definitely diminished in a high percentage of cases. The results paralleled the cholesterol ester figures but the test seemed to be more sensitive in all types of disease of the liver. In acute hepatitis only two cases showed normal hippuric acid excretion, about 3/4 returned to normal and 1/8 remained low. In the chronic cirrhosises this was reversed, about 1/10 recovering to normal and 9/10 remaining low. In the group remaining low, over 1/2 the cases were fatal; namely, eight out of fifteen. All the deaths occurred in this low group and a large majority had an excretion of less than 1 gm. of hippuric acid in 4 hours.

In the gall bladder cases the hippuric test was normal in about 1/10 and low in about 9/10, less than 1/2 of the latter returned to normal. The fact that all the gall bladder cases were jaundiced may explain the high percentage of low hippuric tests on the basis of cholangitis, infection and liver cell damage.

In the tumor cases the hippuric acid output was uniformly low, just as in the acute hepatitis and chronic cirrhosises group.

In the small group of serious obstructive cases in which seven out of eleven were due to cancer, the results of the hippuric test were very similar to the ester per cent, namely, 4/5 were low.

The hippuric acid excretion was low but returned to normal in one case of benign obstruction after operation. In one malignant obstruction it was normal. This is one of the three cases in the whole series where the hippuric acid excretion was normal and the ester cholesterol value low. Two of these were single tests due to the short period of observation of the patient. In the other six cases of malignant obstruction the hippuric acid excretion was low. In one case of benign stricture the hippuric acid excretion was normal and in two cases of common duct stone it was low.

In two cases of hemolytic jaundice the total cholesterol, ester ratio and hippuric acid, and urobilinogen tests were all normal. In the third case the ester per cent started low and improved to just below normal (39%-55%) while the hippuric acid varied from low to normal (0-2.67). Sulphanilimid has been given, which may have caused an acute toxic hepatitis with recovery.

Four to 20 *urobilinogen* tests in the urine were made in practically all cases. The results are condensed in the urobilinogen column. The tests were almost invariably strongly positive in the cases of acute hepatitis if bile was present in the bowel. This was also true in about 80 per cent of the cases of chronic cirrhosis. Urobilinogen was very low or entirely absent in all the cases of complete external obstruction due to cancer. It was present in normal to slightly increased amounts in four cases of benign partial obstruction, in two cases of common duct stone, and in two cases of stricture of common duct. The test was strongly positive in nearly all the gall bladder cases without known obstruction. It was present in normal amounts in two of the three cases of hemolytic jaundice.

In 22 cases *bromsulphalein* tests were made after the jaundice was gone. Retention of this dye ran

TABLE II
Summary of results

Number of Cases		Phos.-Lipids (8-10)		Total Choles. (150-220)			Ester-Per Cent (60-70)			Hippuric (2 1/2-7)		
		Normal	+	Low	Normal	+	Normal	Low to Normal	Low	Normal	Low to Normal	Low
17	ACUTE HEPATITIS	81	19	38	33	24	23	36	36	12	76	12
								72			88	
21	CHRONIC CIRRHOSIS	93	7	45	40	15	55	25	20		10	90
								45			100	
10	GALL BLADDER	50	50	11	67	22	55	34	11	11	34	55
								45			89	
4	TUMORS	80	20		100		100					100
11	OBSTRUCTION	10	90		18	82	19	9	72	18	10	72
								91			82	
3 66	HEMOLYTIC JAUNDICE	100		66	34		66	34		66	31	

almost exactly parallel to lowered hippuric acid excretion. Very slow recovery of normal liver function took place in some cases requiring 6 or 8 months, and the order of recovery was approximately as follows: the ester per cent or the biliary index, later the hippuric acid and bromsulphalein excretion.

The Ivy bleeding time was measured in 27 cases and prolonged bleeding time by this method was commonly associated with poor liver function. In seven fatal cases in which the Ivy test was made, five had prolonged bleeding time (4, 4, 4, 6 and 20 minutes). In a few later cases the prothrombin time in the blood was used instead.

In this paper we have outlined the object of our study and the methods used, and have given in detail the results of the tests in the various diseases of the liver. A second paper will follow entitled "Clinical Value of the Tests" in which the clinical uses of the various tests for diagnosis and prognosis are outlined and compared.

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DISCUSSION

DR. ALBERT M. SNELL (Rochester, Minn.): I was much interested in Doctor White's remarks concerning the usefulness of the hippuric acid test. I think, taking everything into account, that it has given us more information about the general state of the hepatic parenchyma of the jaundiced patient than any other test that we have used. In the presence of jaundice we have found it of great prognostic value. So much so that our surgeons are reluctant to accept the risk of operating on patients whose hippuric acid synthesis is reduced by more than 50 per cent. Our experience with the cholesterol esters ratio has been definitely less satisfactory and we have been unable to correlate the observed changes with any constant clinical syndrome or pathologic change in the liver.

The Effects of Vitamin Deficiency on the Gastro-Intestinal Tract*

By

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THE relationship of the gastro-intestinal tract to states of vitamin deficiency is one of great importance for not only is the gastro-intestinal tract the normal portal of entry for vitamins but its structure and function may be significantly and vitally impaired by deficiencies of them. Two years ago Dr. Snell and I called to your attention the clinical importance of the first phase of this problem in a discussion of the role of alterations in gastro-intestinal function in setting the stage for the development of deficiency states. The present discussion deals with the other phase of this problem namely with the effects of vitamin deficiency on the gastro-intestinal tract.

Experience indicates that fundamentally the most significant roles of the gastro-intestinal tract in predisposing to or conditioning deficiency diseases have to do with an inadequate intake of food, with loss of essential secretions or of food itself, with a lack or decreased production of essential endogenous substances, with inadequate intestinal absorption and perhaps with impaired metabolic activity of certain of the digestive organs. Similarly experience indicates that most of these gastro-intestinal abnormalities may result from deficiency of one or more of the vitamins.

A recapitulation of these facts emphasizes some of the difficulties surrounding a solution of the problem of the effects of vitamin deficiency on the gastro-intestinal tract. In an individual case it may be extremely difficult if not impossible to state whether an alteration in gastro-intestinal function is primary or

whether it is secondary to a state of vitamin deficiency. Other difficulties which are encountered in any attempt to solve this problem are that in man, at least, almost all vitamin deficiency states are multiple; that is they are the result of deficiency of more than one of the vitamins. It is therefore very difficult to determine the effect of deficiency of a single vitamin on the gastro-intestinal function of man. In the third place many of the changes in the gastro-intestinal tract which have been ascribed to vitamin deficiency are non-specific and occur in a large variety of conditions. Many of the observations which have been reported have been based on experiments in animals, on indirect evidence, on symptomatic changes or on therapeutic responses, none of which are entirely satisfactory in clarifying the issue.

Although the problem is one which is difficult to solve it also is one of great importance because many persons subsist on a diet which is borderline in adequacy of various vitamins and particularly of components of the Vitamin B complex. The vicious cycle which may be formed when there is either vitamin deficiency or gastro-intestinal disease may be one of sufficient degree to produce a state of marked vitamin deficiency or it may cause a patient who otherwise would be reasonably well to be precipitated into a state of vitamin deficiency of mild or moderate degree.

Finally the importance of recognizing and understanding this problem lies principally in the fact that vitamin deficiency states are an unusual group of diseases in the respect that they can be entirely prevented

Read at the Annual 1939 Session of the American Gastro-Enterological Association at Atlantic City.

*From the Stanford University School of Medicine.

and that with the exceptions of a few extreme instances they are completely amenable to cure.

The early symptoms of nutritional deficiency are vague and according to Minot (2) a sense of fatigue or lack of energy is common and inefficiency and mental irritability, mild anemia and simple disorders of the digestive tract usually are present.

Haden (3) has classified the lesions of the alimentary tract which are observed as manifestations of deficiency diseases as follows: "(1) anorexia (2) stomatitis (3) glossitis (4) atrophy of tongue (5) achlorhydria (6) loss of specific ferments (7) diarrhea (8) loss of tone of gastro-intestinal tract (9) ulceration of intestine." Other reports of the gastro-intestinal manifestation of deficiency disease which have been made by a number of observers are noted in the subsequent discussion.

PRESENT STUDY

The present study deals with the effects of vitamin deficiency on the gastro-intestinal tract and consists of a summary of available information on this phase of deficiency diseases with some observations in cases in which gastro-intestinal manifestations were a prominent feature. For purposes of a clearer understanding the material has been grouped into sections on the effects of deficiency of each vitamin and the abnormalities associated with deficiency of each vitamin have been grouped into those which are symptomatic, those which produce physiologic changes and those which result in pathologic changes.

THE EFFECT OF DEFICIENCY OF VITAMIN A

Vitamin A is essential for the normal function and integrity of the epithelial tissues of the animal organism. The characteristic changes which follow deficiency of this vitamin have to do with atrophy of the epithelium concerned, the substitution for it of a stratified keratinizing epithelium, followed in many cases by secondary infection of the tissues.

Pathologic changes. In animals. A variety of changes and an absence of changes have been described in the gastro-intestinal tract of Vitamin A deficient animals; they recently have been summarized by Robertson (4). Richards (5) reports that in rats the earliest macroscopic sign of Vitamin A deficiency is in the epithelial lining of the digestive tract which reveals signs of inflammation, hemorrhagic areas and at times ulceration of the stomach. Manville (6) and Cox (7) have reported similar changes in the stomach of rats on a diet deficient in Vitamin A. Wolbach (8) states that in animals with experimental Vitamin A deficiency the mucosa of the stomach and intestines show practically no change and that when changes occur they consist of atrophy which progresses to a state wherein the cells although having the appearance of viability become inert in physiologic activities and in their roles of covering membrane. Changes in the small and large intestine which have been described include atrophy of Brunner's glands, atrophy of the mucous glands, disappearance of goblet cells, chronic inflammatory and proliferative changes, hemorrhagic phenomena and ulceration.

Wolbach and Howe (9) have noted atrophy of the pancreas of the rat in Vitamin A deficiency. Changes which have been noted in the liver include atrophy (Pillat and Chang) (10), hemosiderosis (Wolbach (11), and Sweet and K'ang) (12) and diminution in

size owing to decrease in amount of stored fat and glycogen (Wolbach and Howe (9), Bauercisen) (13).

In man. (Table I). There are surprisingly few reports of pathologic changes in the alimentary tract in cases of Vitamin A deficiency. McCarrison (14) emphasized the occurrence of infections and ulcerations in the gastro-intestinal tract in vitamin deficiency states. However in patients and animals he studied there were deficiencies of other vitamins than of A. In the case of Vitamin A deficiency in an infant reported by Wilson and Dubois (15) no noteworthy abnormality was found in the stomach, pylorus, duodenum, ileum or colon. In the pancreas there were marked changes consisting of inflammation, fibrosis and numerous epithelial-lined cyst-like cavities which apparently were dilated acini. Schiodt (16), Singh (17) and Keefer (18) have reported that atrophy of

TABLE I
Gastro-intestinal manifestations of Vitamin A deficiency

Type of Change	Manifestation	
	Usual	Occasional
Symptomatic	None	Diarrhea
Physiologic	None	Hypochlorhydria Achlorhydria Interference with absorption?
Pathologic	None	1. Atrophy or inflammation of oral, gastric and intestinal mucosa. 2. Atrophy, fibrosis, cyst formation and inflammation of accessory glandular organs. 3. Atrophy, fibrosis, hemosiderosis of liver? 4. Absence or defective enamel and dentine formation of teeth.

the mucosa of the intestinal tract and gastro-enteritis and colitis occur in man in cases of Vitamin A deficiency.

Sweet and K'ang (12) who have had extensive clinical experience with Vitamin A deficiency state in a report of autopsies on seventeen Chinese patients with Vitamin A deficiency, that in five of them the esophagus showed hyperkeratosis and that the digestive tract in all of the cases (17) otherwise was normal. Pathologic changes in the liver of patients with Vitamin A deficiency have not been reported although Wolbach (11) mentions the possibility of hemosiderosis of the liver as a manifestation of deficiency of this vitamin.

Physiologic changes. In animals. Steenbock and his associates (19) have reported that Vitamin A deficiency interferes with the absorption of fat from the intestine of the rat while Kik, Sure and Buchanan (20) note that in rats there is an appreciable decrease in hepatic lipase in this condition.

In man. Reduction in the hydrochloric acid content of the gastric juice in Vitamin A deficiency has been noted by Stepp (21), Boller (22) and Will (23). Pillat and Chang (10) observed achlorhydria in four of fifteen cases of Vitamin A deficiency following stimu-

lation with histamine. In ten of the cases there was definite depression of gastric secretion. Since achlorhydria is rare in the Chinese they considered the findings to be significant. The latter observers reported further that the degree of impairment of gastric function seemed to be related to the duration and severity of the disease of the eye (xerophthalmia) and that the achlorhydria improved when Vitamin A was administered.

Stepp (21) also suggested that Vitamin A deficiency may lead to interference with intestinal absorption in man.

Symptomatic changes. The only gastro-intestinal symptom which has been noted with any frequency in Vitamin A deficiency is diarrhea. Apparently this is not an uncommon accompaniment of xerophthalmia as noted by Stepp (21), Nicholls (24) and Pillat (25). This symptom also has been noted in Vitamin A deficiency in mice, cows and monkeys.

Comment. The paucity of gastro-intestinal symptoms and pathologic changes in cases of Vitamin A deficiency in man is surprising in view of the fact that a large part of the gastro-intestinal tract is made up of epithelial tissue. Since patients with marked degrees of Vitamin A deficiency are observed extremely uncommonly in the United States and since changes in the gastro-intestinal tract do not commonly accompany mild degrees of Vitamin A deficiency clinicians and physiologists in the future probably will not find significant gastro-intestinal alterations in most cases of Vitamin A deficiency which come under their observation. Patients exhibiting such symptoms or lesions have not been observed by me.

Observations which have been made to date suggest that the most likely types of pathologic changes in the gastro-intestinal tract to be expected in Vitamin A deficiency are alterations in the teeth, atrophy or inflammatory changes in the mucosa of the mouth, stomach and intestine and atrophy, cyst formation or inflammation of accessory glandular organs such as the salivary glands, the pancreas and the liver. These changes may interfere with absorption from the intestine, may lead to hypochlorhydria or to achlorhydria or symptomatically may lead to diarrhea. The cause for the diarrhea is not clear. It seems most likely to be related to atrophic or inflammatory changes in the mucosa of the large or small intestine or perhaps to achlorhydria although as noted previously in many cases of keratomalacia the gastro-intestinal tract has appeared to be normal at postmortem examination.

There has been much discussion of the relation of the liver to Vitamin A deficiency. Since the liver is the chief storehouse for Vitamin A it is not surprising that in cases of hepatic disease the Vitamin A content of the liver is diminished or that the vitamin may be absent from it as noted by Moore (26). Haig, Hecht and Patch (27) have indicated that in cases of alcoholic cirrhosis evidence of Vitamin A deficiency is very common. However in cirrhosis and other forms of chronic hepatic disease and in various abnormalities of the gastro-intestinal tract, if deficiency of Vitamin A occurs it seems much more likely that it is secondary to a deficiency in intake, absorption, storage or metabolism of the vitamin rather than primarily the cause of the hepatic or gastro-intestinal disease.

A possible role for Vitamin A deficiency in gastric and duodenal ulcer was suggested by McCarrison (14, 28) and has been confirmed and denied by other

workers. While minute ulcers occur in the stomach of the Vitamin A deficient rat in some cases, convincing evidence that Vitamin A deficiency is related to peptic ulcer in man has not been produced. Indeed it seems quite unlikely that such evidence will be produced because the lesions have not been found in patients with severe Vitamin A deficiency, because most patients with peptic ulcer in this country at least, have an adequate intake of Vitamin A in the diet (milk, cream and butter) and because Vitamin A deficiency frequently leads to hypochlorhydria and achlorhydria. It seems most likely that when deficiency of Vitamin A occurs in association with peptic ulcer that the association is a coincidental one.

THE EFFECT OF DEFICIENCY OF VITAMIN B

Vitamin B has been found to consist of at least four and probably more distinct components. The known components are thiamin chloride, nicotinic acid, riboflavin and Vitamin B₆. As yet sufficient time has not elapsed clearly to distinguish the effects of the individual components on gastro-intestinal function. Consequently in the subsequent discussion mention will be made of the effect of deficiencies of the Vitamin B complex unless there is a reference to a specific component of the complex.

Pathologic changes. In animals. A large variety of pathologic changes in the gastro-intestinal tract of animals on diets deficient in Vitamin B have been reported. Summaries of these findings have been made by Schiødt (16), by Eddy and Dalldorf (29) and by others. In essence the changes consist of atrophy of the lingual papillae, glossitis and stomatitis, diffuse or localized areas of inflammatory disease in the stomach and intestinal tract, atrophy of the intestinal wall (including mucosal and muscle layers) erosion and ulceration particularly of the stomach but also of the intestine, hemorrhage into the stomach or intestine, degeneration of Auerbach's plexus, as well as other less important changes.

In man. (Table II). Glossitis. Stomatitis. Glossitis and stomatitis seem to be an integral part of pellagra, of pernicious anemia and of sprue. In pellagra, in the early stages the most common finding is a reddening of the papillae of the anterior third and tip of the tongue. There may be gradual extension of this process to involve the entire tongue and the buccal mucous membrane with characteristic appearances of a brick or fiery red color and of edema of the tongue which is revealed by marks of the teeth upon it. Associated with this there may be small aphthous ulcers located especially on the base of the tongue and on the buccal mucous membrane. These ulcers usually are covered by a yellowish or white membrane from which Vincent's organisms may be recovered. Often pain of a mild or severe character is associated with the glossitis. In sprue and in pernicious anemia the glossitis most commonly consists of diffuse atrophy of the papillae of the tongue which may or may not be preceded by or associated with some redness and soreness of the tongue and buccal mucous membranes. Somewhat similar changes in the tongue are to be noted in some cases of achlorhydric anemia, anemia of pregnancy, Plummer-Vinson syndrome, in malnutrition attended by dysentery and anemia, intestinal strictures, dibothriocephalus latius infestation and achlorhydria according to Hutter, Middleton and

Steenbock (30). It is quite likely that all of these changes are the result of deficiency of components of the Vitamin B complex or substances closely related to them.

Stomach and Intestine. There is very little clear cut evidence of the pathologic changes in the stomach and intestine in cases of deficiency of Vitamin B. Evidence of the paucity of our knowledge of this subject is indicated by the fact that in a recent article in which he reviewed the pathology of beriberi, Vedder (31) who has had wide experience with this disease fails to mention any gastro-intestinal abnormalities in beriberi. Stepp (21) reports that there is a peculiar tendency to inflammatory reaction in the intestine of patients with Vitamin B deficiency while McCarrison

liver apparently are principally secondary to the associated circulatory failure. Vedder (31) mentions that the liver often has the typical nutmeg character and that some degree of cloudy swelling or fatty degeneration may be found in the liver.

Physiologic changes. In man. (Table II). The outstanding physiologic abnormalities associated with deficiency of Vitamin B may be grouped under the headings of secretory, motor and absorptive disturbances.

Interference with the secretion of hydrochloric acid seems to be a significant change in many cases of pellagra and in other syndromes apparently due to deficiency of the vitamin. Achlorhydria following stimulation with histamine is present in about fifty to sixty-five per cent of cases of pellagra. It occurs also in some cases of beriberi although Kitamura and Shimazono (32) and Keefer (33) are of the opinion that achlorhydria is not associated with this disease. In a study of the gastric acidity of alcohol addicts many of whom exhibited evidence of deficiency states, Joffe and Jolliffe (34) report that in the "uncomplicated" subjects, in polyneuritics and in pellagrins the incidence of achlorhydria was fifteen, twenty-nine and fifty-two per cent respectively. In fact Joffe and Jolliffe (34) have gone so far as to suggest that an achlorhydria preventive factor not identical with Vitamin B₁ probably is present in the Vitamin B complex.

Changes in the secretion of other digestive juices has not been noted in man but Kik, Sure and Buchanan (20) have observed a marked decrease in the digestive efficiency of pancreatic esterase and moderate decrease in the concentration of pancreatic and hepatic lipase in Vitamin B₁ deficiency in the rat.

One of the most interesting although as yet unexplained phases of Vitamin B deficiency is that having to do with the motor activity of the intestine in diseases due to deficiency of Vitamin B or of closely related substances. Observations of the changes have been made principally by roentgenologic methods although a few studies have been reported following insertion of balloons through intestinal fistulas. The changes which have been observed in sprue, in beriberi, in pellagra and in chronic ulcerative colitis are non-specific and consist in essence of distortion of the mucosal pattern and of a variation in the caliber of the intestinal loops.

Mackie and Pound (35), and Snell and Camp (36) as well as others have discussed in detail the roentgenologic appearance of these abnormalities. In some cases the duodenum was dilated and the mucosal markings were thickened. Lower down in the intestinal tract there was a definite smoothing out of the irregular shadows of the valvulae conniventes and clumping of the barium in smooth sausage-like masses. Motility of the barium was considerably interfered with in some cases while in other ones the rapidity of passage of the barium meal was greater than the normal.

Considerable evidence has been presented to suggest that there are disturbances in absorption in cases of Vitamin B deficiency and "related" diseases of the small intestine. Interference with the absorption of fat in cases of sprue has been reported by Barker and Rhoads (37) and other investigators. Abnormalities in absorption of essential hematopoietic substances in similar types of cases also has been suggested. All of this evidence is indirect, however, and only recently has Groen (38) produced more direct evidence that in

TABLE II
Gastro-intestinal alterations in Vitamin B deficiency

Type of Change	Factor	Manifestation
Symptomatic	B ₁	Anorexia
	Nicotinic acid	Diarrhea, sore mouth
	Other?	Constipation, dysphagia, flatulence vomiting? Other vague symptoms
Physiologic	B ₁	Deficient absorption of glucose Achlorhydria? Alteration in muscle tone?
	Nicotinic acid	Achlorhydria? Alteration in muscle tone?
	Other?	Alteration in muscle tone? Achlorhydria? Deficient absorption of glucose and fat
Pathologic	B ₁	Atrophy and inflammation of mucosa?
	Nicotinic acid	Atrophy and inflammation of mucosa? Glossitis, stomatitis, proctitis
	Other?	Atrophy and inflammation of mucosa? Stomatitis?

Other changes which it has been suggested occur in Vitamin B deficiency:

1. Degeneration of Auerbach's plexus
2. Hepatic disease—cirrhosis
3. Peculiar tendency to inflammatory reactions.

(14) in his early observations noted degeneration of Auerbach's plexus in cases of Vitamin B deficiency. Roentgenologic examination of the small intestine of some of these patients suggests the occurrence of edema of the mucosa but whether these changes are characteristic of deficiency of Vitamin B is not clear. Acute inflammatory reactions in the mucosa of the rectum and sigmoid are often to be observed in cases of pellagra.

In addition to the above evidence there are numerous reports of the occurrence of peptic ulcer, of ulcerative colitis and of vague and indefinite types of atrophy and inflammation of the intestinal tract in Vitamin B deficiency.

Pancreas and Liver. In beriberi the pancreas is reported at times to be shrunken and even slightly fibrotic and the islands of Langerhans to be either not affected or hypertrophic. Changes to be noted in the

pernicious anemia, nontropical sprue, "alcoholic" polyneuritis with pellagra there is diminished absorption of glucose as measured quantitatively by means of intubation of the intestine and isolation of a segment of it by means of inflated balloons. Improvement in function with return to a normal condition followed parenteral administration of liver extract in these cases.

The effect of Vitamin B on the liver is not certain. The occurrence of cirrhosis in chronic alcohol addicts with or without accompanying signs of Vitamin B deficiency has suggested to some clinicians the possibility that cirrhosis might be due to deficiency of Vitamin B. Direct evidence to substantiate this opinion has not been presented however. In animals with experimental Vitamin B deficiency atrophy of the liver is said to occur.

Symptoms. *In man.* (Table II). A large number of gastro-intestinal symptoms including anorexia, constipation, diarrhea, dysphagia, flatulence and vomiting have been ascribed to deficiency of components of the Vitamin B complex. Of these symptoms it seems clearly established that anorexia accompanies deficiency of Vitamin B₁ in man as well as in animals. Cowgill (39) and other observers have produced evidence that anorexia is a very early manifestation of Vitamin B₁ deficiency and the studies of Schlutz and Knott (40) indicate that the intake of Vitamin B₁ is related to the appetite of children. Diarrhea is another very common symptom of Vitamin B deficiency. It occurs in pellagra and beriberi in both of which conditions the occurrence of diarrhea has raised the question as to whether or not it led to the development of the deficiency disease or whether the diarrhea was the result of it or both. There is insufficient evidence at the present time to explain other symptoms such as constipation, flatulence, dysphagia and vomiting on the basis of Vitamin B deficiency when they exist without other more definite evidence of deficiency of components of the Vitamin B complex.

Comment. It seems quite clear that thiamin and nicotinic acid are essential for normal functioning of the gastro-intestinal tract. Of the pathologic and physiologic changes and symptoms in deficiency of Vitamin B which have been observed, anorexia apparently is the only one which clearly is related to deficiency of Vitamin B₁. Indeed Strauss (41) recently has pointed out, there is considerable evidence to support the contention that changes in gastro-intestinal tract such as glossitis, achlorhydria and diarrhea are at least in part if not entirely manifestations of deficiency of some portion of the Vitamin B complex other than thiamin. The glossitis, diarrhea, and proctitis of pellagra seem very closely related to deficiency of nicotinic acid for they respond dramatically within a few hours or days to administration of this substance.

It is not clear as yet what factor or factors in liver extract have to do with the changes in the motility and tonus of the intestine and with the interference in absorption of glucose and of fat in patients with sprue, with peripheral neuritis of the alcoholic type, with pernicious anemia and with related conditions. In general these changes in the intestine vary with the intensity of the disease. The relation of them at least in part to deficiency of Vitamin B is suggested by occurrence of them in the above noted conditions

and improvement of them following administration of components of the Vitamin B complex and particularly of liver extract. That other factors such as a deficiency of protein may be significant is suggested by the observations of Ravdin and his associates (63) who recently have demonstrated that changes in intestinal as well as in gastric motility in dogs and patients accompany low values for serum protein.

The mechanism by which deficiency of Vitamin B may lead to the symptomatic and physiologic disturbance is not clear. As Williams and Spies (42) have stated "at the present time it is difficult to understand how an inadequate amount of this Vitamin (B₁) predisposes to gastro-intestinal disturbances." The cause for the anorexia is not evident. One explanation of the achlorhydria accompanying Vitamin B deficiency is that it is a result of atrophy or inflammation of the gastric mucosa. Proof is lacking that interference in intestinal motor activity is the result of degeneration of Auerbach's plexus as McCarrison (14) suggested years ago. Interference with absorption may result from atrophy or inflammatory changes in the intestinal mucosa, changes which apparently are reversible in the majority of cases. The cause of the diarrhea of pellagra is not clear but the dramatic response of that whatever the pathologic changes causing it may be, they are readily reversible ones.

There are a number of observers who believe that lack of Vitamin B may produce peptic ulcer in man, but there is very little evidence in favor of this view. Mackie and Pound (35) have demonstrated roentgenologic changes in the small intestine in many cases of chronic ulcerative colitis. They have suggested that these changes in the small intestine are related to the deficiency states which are observed by them in cases of chronic ulcerative colitis and perhaps that they played a role as a conditioning factor in development of them. The relation of these changes to chronic ulcerative colitis is not entirely clear.

THE EFFECTS OF DEFICIENCY OF VITAMIN C

The gastro-intestinal tract seems to be spared in deficiency of Vitamin C with the exception of changes in the gums which are characteristic of scurvy and of gastro-intestinal hemorrhages which occasionally occur.

Pathologic changes. *In animals.* Pathologic changes in animals with experimental scurvy include abnormalities in the teeth, gingivitis, hemorrhage into the gastric and intestinal mucosa, ulceration of the stomach and intestine, congestion with patches of degeneration of intestinal mucosa, occasional hydropic infiltration of the islets of Langerhans and fatty degeneration of the liver, (Bessey, Menten and King) (43). Gastric and duodenal ulcers are reported to occur with great frequency in guinea pigs on a diet without Vitamin C according to Holst and Frolich (44), McCarrison (45), Magee, Anderson and McCollum (46) and Smith and McConkey (47).

In man. (Table III). Pathologic changes in the gastro-intestinal tract of man in scurvy appear to be limited to the mouth and consist of mild or severe gingivitis. Oozing of blood with hematemeses or melena have been described in cases of scurvy in man and presumably they occur from small lesions in the stomach or intestine. Pathologic changes in the

not an accompaniment of scurvy. Musser and Sodeman (48) recently observed very severe proctitis in a patient with Vitamin C deficiency.

Physiologic effects. In animals. According to Einhauser (49) Vitamin C is a normal constituent of the wall of the intestine and serves a detoxifying and protecting function. Shimamura (50) reports that in guinea pigs on a scorbutic diet the glycogen content of the liver is low and that it would be increased up to but not beyond a certain level by daily administration of Vitamin C. In a study of the motility and permeability of the intestine by means of a variety of different methods Smith (64) could find no significant impairment in acute or chronic scurvy.

In man. There is very little evidence of physiologic impairment of the gastro-intestinal tract in scurvy in man. Coffé and Dulee (51) have reported that in normal subjects intravenous administration of Vitamin C increased the volume and the concentration of free hydrochloric acid and of total acid in the gastric con-

TABLE III

The gastro-intestinal alterations in Vitamin C deficiency

Type of Change	Manifestation	
	Usual	Occasional
Symptomatic	Gingivitis Anorexia	Diarrhea Hemorrhage
Physiologic	None noted	None noted
Pathologic	Infected, spongy, bleeding gums	Dental caries Intestinal hemorrhage

tent although it had no such effect in a case of pernicious anemia. Absorption of glucose from the small intestine of two patients with scurvy was found to be normal by Groen (38).

Symptoms. The outstanding gastro-intestinal symptoms in scurvy are related to gingivitis. Anorexia and diarrhea may be present; occasionally there may be some gross bleeding.

Comment. Although Vitamin C apparently is essential for all living cells, there is very little evidence of significant gastro-intestinal alterations in Vitamin C deficiency with the exception of gingivitis and perhaps occasionally of bleeding. However a great deal of controversy has surrounded the possible role of Vitamin C deficiency in cases of peptic ulcer and in bleeding from ulcer and other lesions. Numerous reports in the literature have pointed to the occurrence of ulcers having some of the characteristics of peptic ulcer in the stomach and duodenum and intestine of animals with experimental scurvy and there has been repeated confirmation of the observation that low values for Vitamin C in the blood are the rule for patients with peptic ulcer. The studies of Ingalls and Warren (52), Bourne (53), and Rivers and Carlson (54) agree that patients with peptic ulcer, even those who may be receiving an approved diet for ulcer, have lower levels of ascorbic acid in the blood and urine than have normal persons. Elder and Emery (55) have analyzed the eating habits of twenty-five patients with ulcer and of twenty-five control patients and have come to

the conclusion that peptic ulcer is not a deficiency disease in the sense in which this term ordinarily is used. Despite all of these findings there is considerable doubt in the minds of many clinicians as to the relation of deficiency of Vitamin C to peptic ulcer and certainly further studies will be required to settle this point. It seems quite reasonable to agree with Jones and his collaborators (56) that it is highly probable that the findings just noted represent the results of a deficiency secondary to the original ulcer condition, rather than that there is a causative relation to the formation of ulcer.

The relation of hemorrhage from the gastro-intestinal tract to deficiency of Vitamin C remains unsettled. The observations of Portnoy and Wilkinson (57) indicate that patients who have peptic ulcer and bleed from them and especially those who have hematemesis have marked Vitamin C deficiency—in fact such cases usually present more evidence of Vitamin C deficiency than do patients with peptic ulcer who have not bled. The likelihood that this result is secondary to a diet deficient in Vitamin C is great but further evidence will be required before this point can be settled definitely.

THE EFFECT OF DEFICIENCY OF VITAMIN D

Although diseases of the mucosa of the small intestine and interference with the flow of bile into the duodenum may seriously impair absorption of Vitamin D and although the liver appears to be essential for the anti-rachitic efficiency of Vitamin D in animals there is very little if any evidence that deficiency of Vitamin D leads to impairment in gastro-intestinal function or structure. Atony of the intestine has been described as an accompaniment of rickets but the relation of it to deficiency of Vitamin D is not clear. Yoder (58) has produced evidence from experiments on rats which he feels indicates that "there must be a minimal requirement of Vitamin D by the digestive tract for a tonicity which can maintain either a decreased intestinal volume or increased motility."

THE EFFECT OF DEFICIENCY OF VITAMIN E

Evidence is lacking that deficiency of Vitamin E results in significant gastro-intestinal abnormalities.

THE EFFECT OF DEFICIENCY OF VITAMIN K

Considerable evidence has accumulated to indicate that there is a relation between deficiency of Vitamin K and the hemorrhagic tendency in jaundice. In cases of Vitamin K deficiency in chicks and perhaps also in other animals and in man there is a deficiency of prothrombin in the blood plasma. This effect may be brought about by a variety of mechanisms including a diet deficient in Vitamin K, interference with absorption of the vitamin because of absence of bile in the intestine, or as a result of hepatic damage with impairment in the fabrication, storage or activation of prothrombin which seems to occur in the liver. Evidence has not been presented to suggest that any abnormality in gastro-intestinal function or structure occurs as a result of Vitamin K deficiency with the exception of those changes associated with bleeding.

THE EFFECTS OF DEFICIENCY OF ANTI-GIZZARD EROSION FACTOR

In his original studies of the hemorrhagic disease of chicks, Dam (59) reported the occurrence of erosion

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DISCUSSION

DR. MARTIN G. VORHAUS (New York): There is no question that a paper on this subject is timely before this group particularly in regard to the question of symptoms of deficiency states. As Dr. Wilbur has shown, one of the most important in the group is the symptom of anorexia. All experimenters in the vitamin field agree that in B deficiency anorexia is an outstanding manifestation, but, unfortunately, the clinician has taken the point of view that the administration of the B group is an excellent method of combating this symptom.

In our clinical experience we have found that the reverse is true. We have been able to stimulate appetite in less than 15 per cent of cases who have received thiamin in large doses over a long period of time. It is important to stress this point since a great deal has been written upon the value of thiamin in the treatment of anorexia, and the clinician who accepts these facts is bound to find that his clinical experience is extremely disappointing.

The same thing is true in consideration of constipation. Though it is frequently present in animals, less than 1 per cent (and a great deal less than 1 per cent) of the cases of constipation are improved by administration of the Vitamin B complex.

The Clinical Value of Quantitative Vitamin Determinations*

By

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and

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With the assistance of

RUTH BACH, M.A.

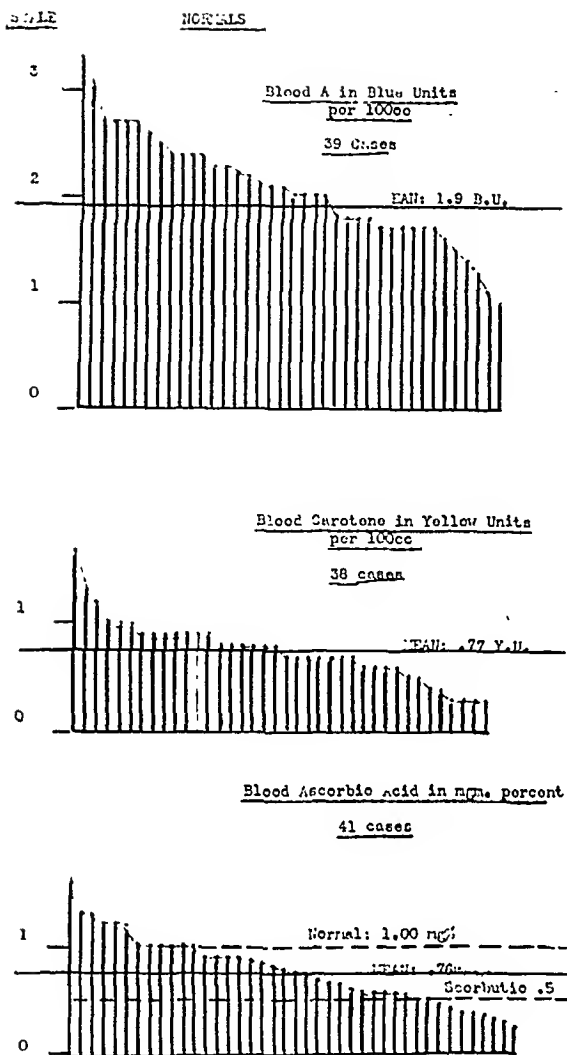
NEW YORK, NEW YORK

THE rapid increase in knowledge of the chemistry of the vitamins has given new impetus to studies of nutrition. Quantitative chemical and physical methods are being developed which are applicable to clinical practice. These have greatly broadened the scope of the field. While the disease states resulting from extreme deprivation of certain vitamins have long been recognized, we have had no means to explore border-line conditions nor indeed to recognize them.

*From the Gray Laboratory of the Roosevelt Hospital. Read at the Annual 1939 Session of the American Gastro-Enterological Association at Atlantic City.

They constitute a field of medicine which is almost wholly unexplored.

The experimental pathology of the avitaminoses when correlated with observed human pathology indicate the fundamental importance of adequate supplies of these essential food factors. Dalldorf and Eddy (1) have presented a critical evaluation of this evidence. These structural changes inevitably are accompanied by disturbances of normal physiology—affecting many organs. The physical signs and symptoms at present associated with the avitaminoses are indicative of



Graph 1

severe grades of deficiency. It is assumed that the individual who presents none of these phenomena is in a satisfactory state of nutrition. This is not necessarily the case. Less advanced grades of vitamin deficiency lacking characteristic signs and symptoms unquestionably pass unrecognized. It is not permissible to conclude from the type of negative evidence so far available, that the lesser degrees of deficiency do not militate against optimum health on the one hand, and contribute to disease on the other.

The exact requirements for the particular vitamins are unknown. The estimated requirements are based upon amounts apparently sufficient to protect against deficiency disease supplemented to provide a factor of safety. These values at best are only approximations. They are not valid criteria of adequacy especially in the presence of clinical conditions associated with faulty digestion, defective absorption from the intestinal tract, liver disease, or excessive metabolic requirements. It is evident that great variation in individual needs must occur. It is likewise evident that rational

and successful therapy must be based upon accurate standards of normal vitamin saturation, and upon direct quantitative methods which can be used for clinical investigation. Such tests are being developed, and although imperfect they afford a preliminary technique for exploration of deficiencies of Vitamin A; pro-Vitamin A, carotene; Vitamin C, and Vitamin K.

There is a paucity of literature dealing with blood values of Vitamin A. Menken (2) has reported the equivalent of 0 to 8.4 Lovibond blue units per 100 cc. Other reports which attempt to translate the colorimetric readings into terms of vitamin units are not comparable.

Data on blood carotene values are more numerous but show marked variation. Clausen (3) reported a fairly constant level at 0.08 mg. per 100 cc., the equivalent of 1.3 Lovibond yellow units, in normal children over two years of age.

Normal blood values for Vitamin C have been fairly well established by reports from many laboratories. Abt and Farmer (4) in a recent critical review, state that healthy persons taking what is considered to be an adequate intake of Vitamin C yield plasma values of 0.7 mgs. per 100 cc. or higher. Values below this level they consider subnormal, or at least suboptimal. According to them active scurvy may occur with a Vitamin C level up to 0.4 to 0.5 mgs. per 100 cc.

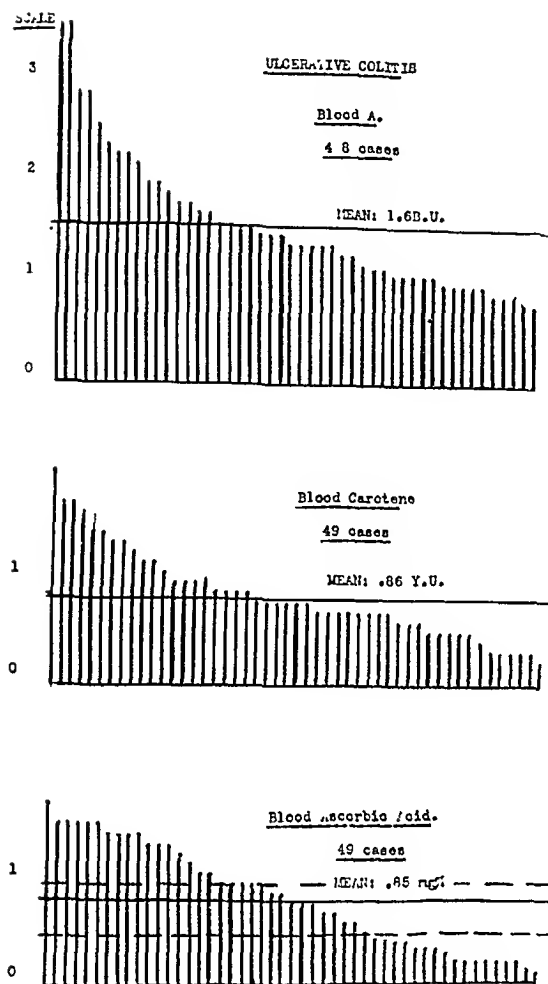
An additional antihemorrhagic dietary factor, Vitamin K originally described by Dam (5) has recently received much attention. Lack of this substance is associated with deficiency of prothrombin in the plasma of chicks with hemorrhagic disease, and of dogs and of man with various pathologic conditions of the biliary tract and the liver. Snell, Butt and Osterberg (6) have shown that oral administration of this fat soluble factor in the presence of adequate amounts of bile salts will increase the concentration of prothrombin and thereby reduce the clotting time of the blood. They have likewise shown that determination of prothrombin time may be used as an index of prothrombin concentration and indirectly, therefore, a measurement of Vitamin K deficiency.

MATERIAL

We have been impressed with the importance of mixed deficiency states occurring in the course of certain diseases, notably chronic ulcerative colitis and sprue (7, 8, 9). During the past year determinations of blood carotene, Vitamin A, Vitamin C and Vitamin K have been included among the routine studies of a considerable group of individuals. This report is based upon our findings in forty-one apparently normal healthy adults and two hundred and sixteen patients seen in hospital, dispensary, and private practice in New York City. The patient group includes forty-nine cases of chronic ulcerative colitis, forty-six cases of peptic ulcer, and one hundred and twenty-one miscellaneous ward cases.

METHODS

Plasma Vitamin A determinations have been done by the modification of Van Eckelan's method described by Menken (2). Readings are made against the blue plates of the Lovibond tintometer. Since the color reaction is transitory and since no completely satisfactory conversion factor for translation into units of



Graph 2

Vitamin A is available, results are expressed as Lovibond Blue Units (LBU).

The carotene determinations have been made by the same technique, by extraction and comparison with the yellow standards of the Lovibond Tintometer. It has seemed desirable to express results in terms of Lovibond Yellow Units (LYU) rather than to translate them into milligrams of carotene by reference to the Ferguson (10) curve.

Vitamin C determinations have been made by the method of Farmer and Abt (11). Results are expressed in terms of milligrams per 100 cc.

The Vitamin K status has been estimated by measurements of prothrombin time using the methods of Quick, Stanley-Brown and Bancroft (12) and of Quick (13). Results are expressed in seconds. The upper limit of normal for these methods is thirty seconds and fifteen seconds respectively.

FINDINGS IN NORMAL ADULTS

Forty-one apparently normal healthy adults were studied to calibrate the methods, and to establish normal ranges for purposes of comparison. Blood Vitamin C determinations were done on all, Vitamin

A in thirty-nine, and carotene in thirty-eight. Casual non-fasting determinations were made on each individual and subsequently the tests were repeated using morning fasting blood from each subject. The casual specimens revealed higher average values for each substance tested, larger ranges, and larger standard

TABLE I
Fasting normals

Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	39	38	41
Ave. Finding	1.9 Blue units	0.77 Yellow units	0.76 mg. %
Range	2.3—1.0	1.7—0.3	1.60—0.25
St. Deviation	0.55	0.29	0.32
St. Deviation Means	0.08	0.04	0.05
Probable Error	0.05	0.03	0.03

deviations. Consequently the fasting values have been accepted as more significant and have been utilized throughout.

The thirty-nine normals tested gave an average Vitamin A content equivalent to 1.9 LBU with a standard deviation of ± 0.55 . The extremes were 1.0 LBU and 3.3 LBU. (Graph 1).

The blood carotene content in the thirty-eight normals averaged 0.77 LYU with a standard deviation of ± 0.29 . The extremes were 0.3 and 1.7 LYU.

The Vitamin C values in forty-one normals averaged 0.76 mgs. per 100 cc. with a standard deviation of 0.32. The extremes were 0.25 mgs. per 100 cc. and 1.60 mgs. per 100 cc.

ULCERATIVE COLITIS

Forty-nine cases of chronic ulcerative colitis have been studied in similar fashion. (Graph 2). The average Vitamin A value was found to be equivalent to 1.6 LBU; the standard deviation ± 0.67 , and the range 0.8 LBU to 3.6 LBU. Contrasting these findings

TABLE II
Ulcerative colitis cases

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	48	47	49
Ave. Finding	1.6 Blue units	0.85 Yellow units	0.85 mg. %
Range	3.6—0.8	2.1—0.2	1.8—0.1
St. Deviation	0.67	0.41	0.53
St. Deviation Means	0.10	0.06	0.08
Probable Error	0.06	0.04	0.05

with those in the normal control group, the average is somewhat lower, the range is greater, and the lowest value observed is lower than any in the normal group. The average carotene content, 0.86 LYU is somewhat above that observed in the control group, the range is greater, the standard deviation is larger, and the lowest value is below that observed in normals. The average Vitamin C content, 0.85 mgs. per 100 cc. is likewise above the average value observed in the

normal group, the range is greater, the standard deviation larger, and the lowest value below that found in the controls.

Forty-six cases of peptic ulcer have been studied by the same technique. (Graph 3). All were hospitalized for treatment. The observations to be presented represent the first determinations after admission to the

TABLE III
Ulcer cases

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	46	46	43
Ave. Finding	1.5 Blue units	0.87 Yellow units	0.51 mg. %
Range	2.5 — 0.7	2.3 — 0.2	1.60 — 0.1
St. Deviation	0.45	0.40	0.13
St. Deviation Means	0.07	0.06	0.02
Probable Error	0.01	0.01	0.01

wards. The average Vitamin A value, equivalent to 1.5 LBU is lower than that in the normal group, or that found in the colitis group, the range is less, the low value is below in either of the other groups, and the standard deviation is lower. The average carotene value, however, 0.87 LYU is higher and the range is greater. The lowest value is below that in the control group and is equal to that in the colitis group. The average Vitamin C level, however, of 0.51 mgs. per 100 cc. is lower than in either group and lies at the scorbutic borderline. There is little difference in comparison of ranges. The standard deviation, however, is lower.

One hundred and twenty-one miscellaneous ward patients have been studied in similar fashion as a second control and are presented without respect to diagnosis and without reference to duration of hospital residence. (Graph 4). Vitamin A determinations have been made on one hundred and fourteen. The average, equivalent to 1.5 LBU, corresponds to the

TABLE IV
Miscellaneous ward patients

FASTING VALUES			
Vitamins Tested	Vitamin A	Carotene	Vitamin C
No. Cases	116	121	105
Ave. Finding	1.5 Blue units	0.87 Yellow units	0.64 mg. %
Range	3.5 — 0.6	3.2 — 0.2	2.90 — 0.10
St. Deviation	0.19	0.53	0.45
St. Deviation Means	0.02	0.05	0.05
Probable Error	0.01	0.03	0.03

finding in the ulcer cases and is below the level of the normal and the colitis groups. The range is greater than in the other three groups. The lowest value is lower, and the standard deviation is less.

The carotene level, 0.87 LYU, is comparable to those in the ulcer and colitis groups, and is above the level observed in the normal controls. The range and the

standard deviation are greater than in any of the three groups. The average Vitamin C level, 0.64 mgs. per 100 cc. is intermediate between those of the ulcer and the colitis cases. The range, however, is greater than that in any of the other groups.

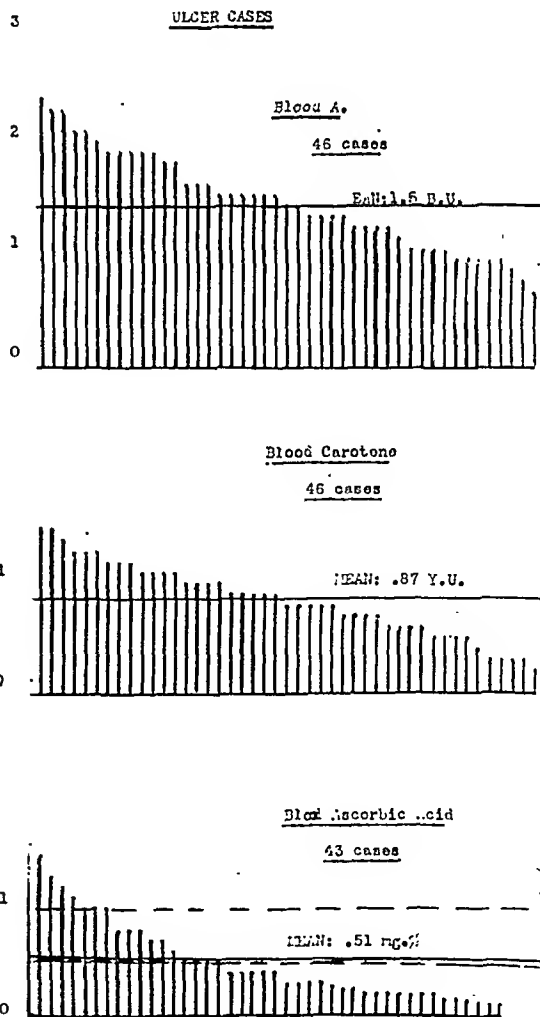
VITAMIN K

Prothrombin determinations have been made on sixty-nine miscellaneous cases. Three individuals have shown a definite elevation of prothrombin time. It is of interest to note that jaundice was not present.

DISCUSSION

The methods used for estimation of blood Vitamin A and carotene are admittedly inexact as in any colorimetric procedure which is based upon a transitory end point. This potential source of error is probably magnified to some extent when readings are made by eye rather than by photoelectric equipment. With practice, however, satisfactory uniformity of results can be obtained on duplicate specimens. Since there is an inherent and unavoidable error in the method it

SCALE



Graph 3

has seemed best not to magnify this error by the effort to translate blue units into U.S.P. units of Vitamin A, and yellow units into milligrams of carotene. Since exact human standards are either unknown or still subject to discussion it was decided to use the values observed in our normal group as the standard for comparison. A chart has been constructed on which are plotted as zones the "A," carotene, and "C" values obtained from the normal group. Each of these zones

therefore is not an accurate index of saturation or depletion. Similarly the plasma carotene appears to be a measure of the difference between rate of absorption and rate of conversion to Vitamin A rather than an index of reserve or intake.

The normal range for blood Vitamin C is well established.

We have no basis for contrasting the Vitamin A values in our normal controls with other findings reported in the literature. The blood carotene average is definitely below the level reported by Clausen (3) for normal children. Our control group as a whole appears somewhat deficient in Vitamin C. Ten had 0.5 mgs. per 100 cc. or less. Only twelve reached or exceeded 1.0 mgs. per 100 cc.

The average values observed in the cases of chronic ulcerative colitis probably do not present a true picture. Many of these individuals had been under observation for considerable periods in the Outpatient Department where they had received careful dietetic instruction from a trained dietitian. Moreover in most instances they were receiving supplemental vitamin medication. It is significant, however, that the lowest values for "A" and "C" were below the lowest values observed in the control group.

The findings in the ulcer cases, on the other hand, are not weighted by previously given vitamin medication or carefully supervised diets. The observations in this group were made on consecutive ward admissions within twenty-four to forty-eight hours after entry into hospital. The average values for Vitamin A and Vitamin C are distinctly lower than those in the control group, and the minimal values likewise are lower. Our Vitamin C findings confirm the previously reported results of Portnoy and Wilkinson (15) and Lazarus (16).

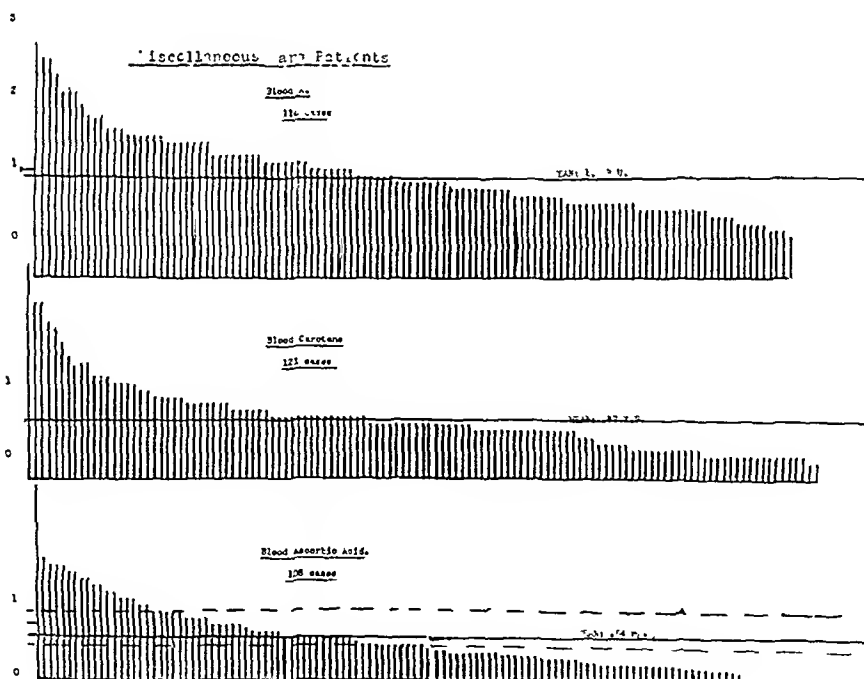
The data obtained from the miscellaneous group do

Vitamin K

No. cases tested	69	Prothrombin Time	Diagnosis
Elevated Prothrombin time	3		
1. S.B.		3 min. 12 sec	Ulcerative Colitis
2. M.A.		6 min —no clot	Chronic Enteritis
3. E.P.		1 min 3 sec.	Sprue

is derived by applying the standard deviation to the average.

The resulting "normal" chart (Graph 5) however is undoubtedly normal in a relative sense only. Present information does not permit definition of the normal level of blood Vitamin A or carotene. Since several of our control group revealed Vitamin C levels below the scorbutic threshold it is improbable that the lowest values for Vitamin A and carotene represent optimal values. Furthermore, requirements undoubtedly vary under differing physiologic and pathologic conditions. Moreover, Bessey and Wolbach (14) have pointed out that the concentration of Vitamin A in the blood is independent of the amount stored in the liver and



Graph 4

not permit of any definite conclusions. In general the values fall between the ulcer cases on the one hand and the colitis and normal groups on the other. This finding is to be expected in individuals either chronically or acutely sick who have not been receiving supplemental vitamin medication. One striking finding, however, in this group, the frequency of low Vitamin C levels, is well shown on Graph 4. This may be explained by poor diets prior to entry, increased metabolic demands, or hospital diet which is inadequate to meet the apparent high requirements of these patients.

It is of interest to note that the carotene values in the colitis, the ulcer, and the miscellaneous groups, are definitely above the average of the normal groups. The significance of this is not clear.

Despite the sources of error at present inherent in blood Vitamin A determinations, the findings in our

The past history is irrelevant except for chronic sinusitis, bleeding gums at times and cutaneous ecchymoses following slight trauma.

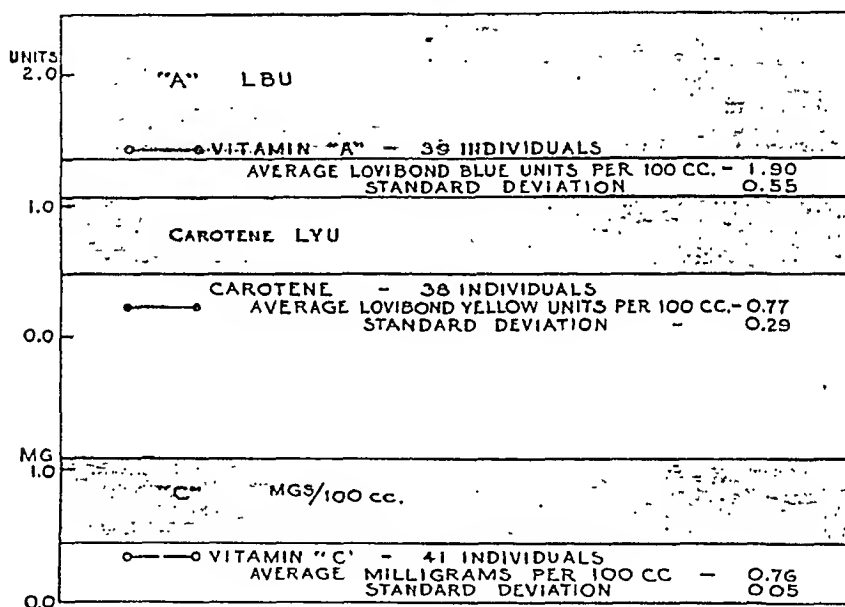
Physical examination revealed a poorly nourished pale, chronically sick young woman. The tongue was normal and the teeth and gums in good condition. No abnormalities of the skin were noted. The heart and lungs and abdomen were negative. Proctoscopic examination revealed a swollen acutely inflamed mucosa oozing blood freely.

She was followed in the Outpatient Department for two weeks and then admitted on January 11th because of increasing weakness, persistent diarrhea and profuse rectal bleeding. On two occasions just prior to hospitalization she vomited small amounts of blood.

TREATMENT

At the first visit to the Outpatient Department she was referred to the dietitian and instructed to take a diet containing adequate sources of Vitamin C. During the second week Vitamin A, 26,600 units, in the form of oleum per-

FASTING BLOOD VITAMIN VALUES - NORMAL INDIVIDUALS



Graph 5

hands parallel the clinical condition in many patients. Low values have been amply confirmed by correlation with well recognized physical signs. The value of repeated Vitamin A, C and occasionally K estimations is illustrated by the following cases.

CASE ABSTRACTS

R. P.: Age 30. The patient is a thirty year old Italian American housewife who was first seen on December 28, 1938. Four years previously she developed a gradually increasing diarrhea with bleeding from the colon. This attack subsided in the course of a month and was followed by a year of freedom from symptoms in which she gained 18 pounds. The second attack followed oophorectomy and appendectomy. A third episode occurred 2 years later and again cleared up in a reasonable period of time. The fourth attack began five weeks prior to admission with gradually increasing diarrhea with mucus and blood in the stools. Since the onset of this last attack she had been on a restricted soft diet with boiled meats but had had no fruit juices, fruits or vegetables.

comorphum were given daily. From January 11th to January 19th treatment was by diet alone. On the latter date Vitamin A 13,300 units daily in the form of oleum percomorphum was added and continued throughout the period of observation. No other supplemental sources of Vitamins A or C or carotene were given. (Graph 6).

VITAMIN ASSAYS

On December 29th the fasting blood values were as follows: Vitamin C 0.2 mgs. per 100 cc.; Vitamin A 1.1 Lovibond blue unit equivalents; Carotene 0.6 Lovibond yellow unit equivalents. On January 11th and 12th the Vitamin C level had risen to 1.1 mgs. per 100 cc. Thereafter it remained at normal or saturation levels. The prothrombin time on January 11th was found to be 47 seconds falling to normal on January 17th.

The blood Vitamin A remained at the low level of 1.1 LBU per 100 cc. through January 19th. Daily administration of 13,300 units of "A" thereafter was followed by progressive rise to the normal zone.

The blood carotene curve irregularly parallels the Vitamin "A" curve.

COMMENT

This patient's diet was grossly deficient in sources of Vitamins C and K and probably lacking as well in thiamin, A and D. On dietary management alone the blood Vitamin "C" returned to normal levels within two weeks. The prothrombin time likewise fell to normal. Cessation of rectal bleeding coincided roughly with the restoration of these values to normal. Daily administration of 13,300 units of Vitamin A in the form of oleum percomorphum was accompanied by a progressive rise of the blood "A" values toward normal levels.

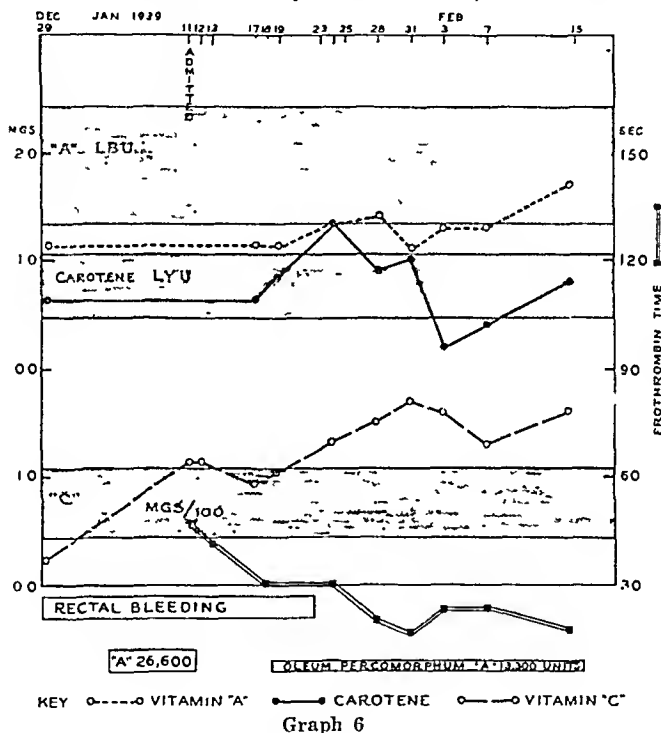
This patient therefore exhibited a multiple deficiency involving at least Vitamins A and C. The slightly but definitely elevated prothrombin time noted after two weeks on a properly balanced diet, and the relatively close association in time between cessation of rectal bleeding

out fever and without evidence of organic cardiac disease. The ankle jerks were not obtainable. Proctoscopy revealed an advanced but relatively quiescent ulcerative colitis without evidence of bleeding. Barium enema showed total involvement of the colon. X-ray examination of the skeleton is reported as follows: "Skeletal epiphyses were examined and the development is in keeping with that of a twelve year individual." (Graph 7).

VITAMIN ASSAY

Vitamin assay on admission revealed a normal blood carotene and Vitamin "C," and a very low Vitamin A. The values were 0.9 LYU, 1.1 mgs. per 100 cc. and 1.0 LBU respectively. The prothrombin time 49 seconds, was slightly elevated. In view of these findings the base diet was supplemented by Vitamin A 26,600 units per day in the form of oleum percomorphum. This was followed by a definite rise in the blood A curve which however levelled

R P AGE 30 ULCERATIVE COLITIS, DEFECTIVE DIET, RECTAL BLEEDING



and normal prothrombin levels suggest a Vitamin K deficiency as well. Improvement in the blood vitamin levels was accompanied by definite general clinical improvement.

R. W.: The patient is a seventeen year old American boy who was admitted to the hospital on January 15, 1939. Five years previously he developed what was diagnosed as chronic ulcerative colitis following an attack of typhoid fever. There were repeated recurrences. During the ten months prior to admission he had had persistent diarrhea without gross blood in the stools. During the past two years he lost thirty pounds in weight.

Physical examination revealed a greatly emaciated underdeveloped boy. Stature was much below normal. The genitalia were undeveloped and there was no axillary or pubic hair. The tongue was definitely smooth but not red or inflamed. The skin was exceedingly dry, harsh, and scaly, and the mucous membranes pale. Two chronic ulcers of four months duration were present in the skin of the abdomen. There was a marked tachycardia with-

off at 1.5 LBU. Because of this the oleum percomorphum by mouth was supplemented by daily inunctions of 15 cc. of cod liver oil. This combined therapy was given from January 31st to February 7th inclusive when both were discontinued. On the latter date the blood A had reached 1.7 LBU and despite ileostomy the following day the "A" values rose to 2.1 LBU, at which time oral administration was resumed.

The blood carotene curve varied irregularly throughout the period of observation.

The blood Vitamin "C" fell slowly following admission to 0.6 mgs. per cent. At this time 1.0 gms. of cevitamic acid by mouth was given daily through February 7th. The curve promptly rose to the normal range, falling again in the post-operative period to 0.3 mgs. per 100 cc.

The prothrombin time fell to normal without supplemental medication.

The patient was discharged on March 23rd much improved, having gained twelve pounds.

COMMENT

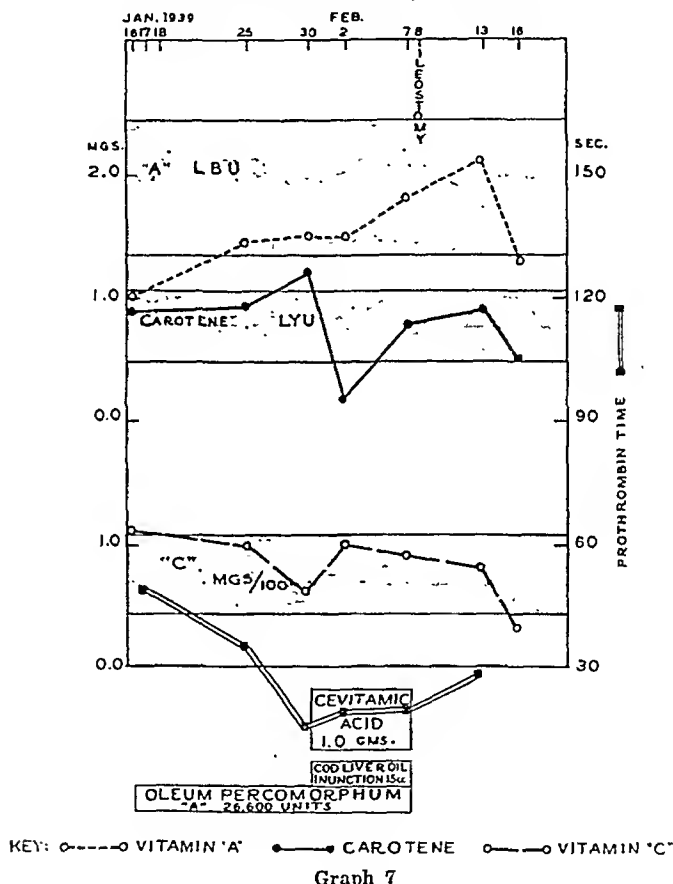
This patient on admission presented clinical evidence of advanced deficiency disease characterized by arrested growth, emaciation, anemia, delayed puberty, arrest of bone development and the skin changes associated with Vitamin A deficiency. The bone changes demonstrated by X-ray are characteristic of recurrent rickets and also of experimental "A" deficiency in animals. Treatment was guided by the vitamin assays and the date of operation based upon the observed curves. The unusually smooth convalescence we attribute in no small part to the correction of the observed deficiencies.

examination revealed an acute diffuse inflammatory process throughout the visualized area with moderate bleeding. Barium enema showed involvement of the entire colon. There was a moderately severe anemia. Macrocytes and nucleated red cells were seen in the stained blood film.

COURSE

During the ensuing weeks he developed a variety of complications. The tongue and buccal mucosa became red, inflamed and painful, presenting the characteristic appearances of acute pellagra. Parenteral liver extract (Lilly 343) failed to control the oral condition until 600 mgs. of nicotinic acid daily was added. Two perirectal abscesses required surgical drainage. The general condition became increasingly unsatisfactory, with progres-

R.W. AGE 17: ULCERATIVE COLITIS, GROWTH FAILURE, DELAYED PUBERTY, MALNUTRITION



S. B.: The patient was a twenty-one year old American male who was admitted to the hospital on September 13, 1938. Six weeks previously he developed a gradually increasing watery diarrhea, weakness and progressive loss of weight.

The past history was non-revealing.

On admission he showed marked emaciation and pallor. The tongue was smooth but not inflamed and there were scattered aphthous ulcers on the buccal mucosa. The skin was very dry and slightly hyperkeratotic. Heart and lungs were negative. There was tenderness over the colon and a palpable dilated cecum. Hyperesthesia and paresthesia were noted over the dorsum of the right foot. The right patellar reflex was less active than the left. Proctoscopic

sive weight loss, septic temperature curve, and evidence of renal irritation. By mid-December surgery seemed to offer the only hope of survival. Recognizing the seriousness of the risk ileostomy was performed on December 10th. Six days later he developed what appeared to be acute scurvy. The ileostomy drainage consisted of tarry material giving a strongly positive benzedine reaction, there was blood in the urine, the entire body was studded with cutaneous petechiae, and there was a massive subcutaneous hemorrhage in the left leg. There was no reduction of blood platelets. The appearance of these signs was accompanied by shock which was controlled by transfusion. Death occurred nine days later from inanition without evidence of further hemorrhage. (Graph 8).

VITAMIN ASSAYS

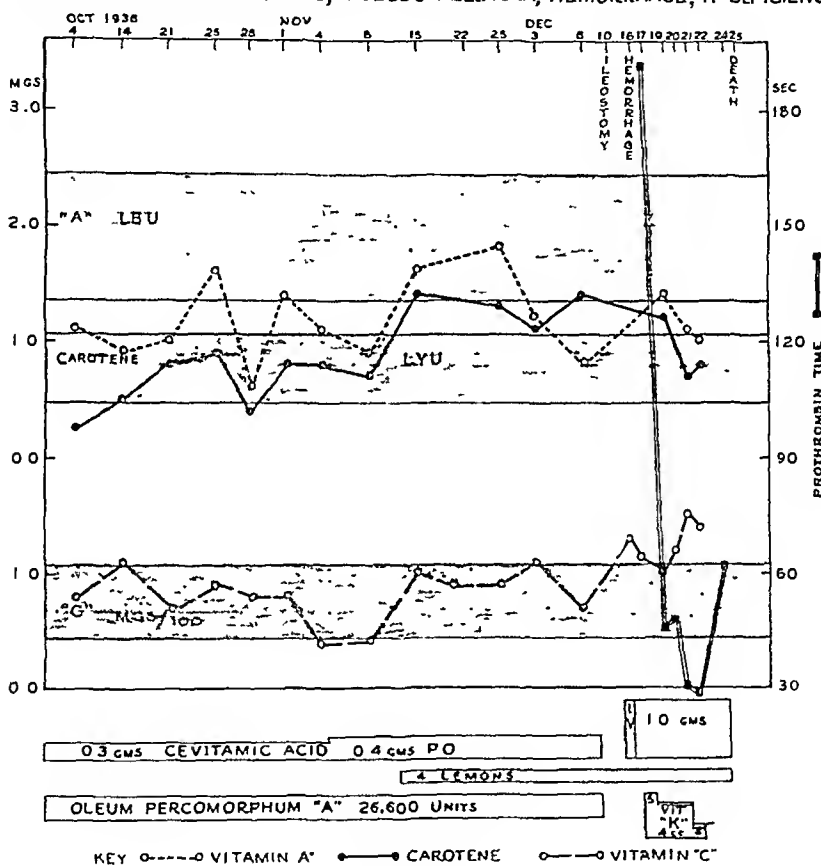
It was impossible to do a blood vitamin assay until two weeks after admission. Because of the obvious malnutrition and the rectal bleeding he was placed at once on 300 mgs. cevitamic acid by mouth daily and 26,600 units of Vitamin "A" in the form of oleum percomorphum. On October 4th the blood Vitamin A and carotene were both at low levels, 1.1 LBU and 0.25 LYU respectively. The Vitamin C content was 0.8 mgs. per 100 cc. During the period of observation the Vitamin A curve fluctuated irregularly seldom reaching normal values. The initial dosage of oleum percomorphum was continued unchanged. The blood carotene curve showed a sustained rise until operation on December 10th when it dropped again moderately. The Vitamin C content remained at normal levels

when it was found to be 1.3 mgs. per 100 cc. The following day the prothrombin time was found to be 192 seconds. Through the courtesy of E. R. Squibb & Co. we were able to obtain a Vitamin "K" concentrate containing 500 units per cc. Five cc. were given by mouth on December 18th and four cc. 19th, 20th and 21st and two cc. on the 22nd. The prothrombin time was thirty-one seconds on the 21st and twenty-nine seconds on the 22nd. On December 21st, two days after discontinuing the "K" concentrate, the prothrombin time had again risen to 62 seconds. Bilc salts were not administered.

COMMENT

This patient presented a severe mixed deficiency state characterized clinically by pseudo-pellagra, macrocytic

S.B. AGE 21—ULCERATIVE COLITIS, PSEUDO-PELLAGRA, HEMORRHAGE, "K" DEFICIENCY



Graph 8

until November 4th when it had fallen to 0.4 mgs. per 100 cc. The daily dosage of cevitamic acid was then increased to 400 mgs. This was followed by a rise of the curve into the normal range. On December 8th, 2 days prior to operation, the blood "C" was 0.7 mgs. per 100 cc. For a month before this date the diet had been supplemented by the juice of four lemons daily. All medications were stopped the day of operation. Fluids by mouth including fruit juices were resumed the day of operation and soft diet on the 13th.

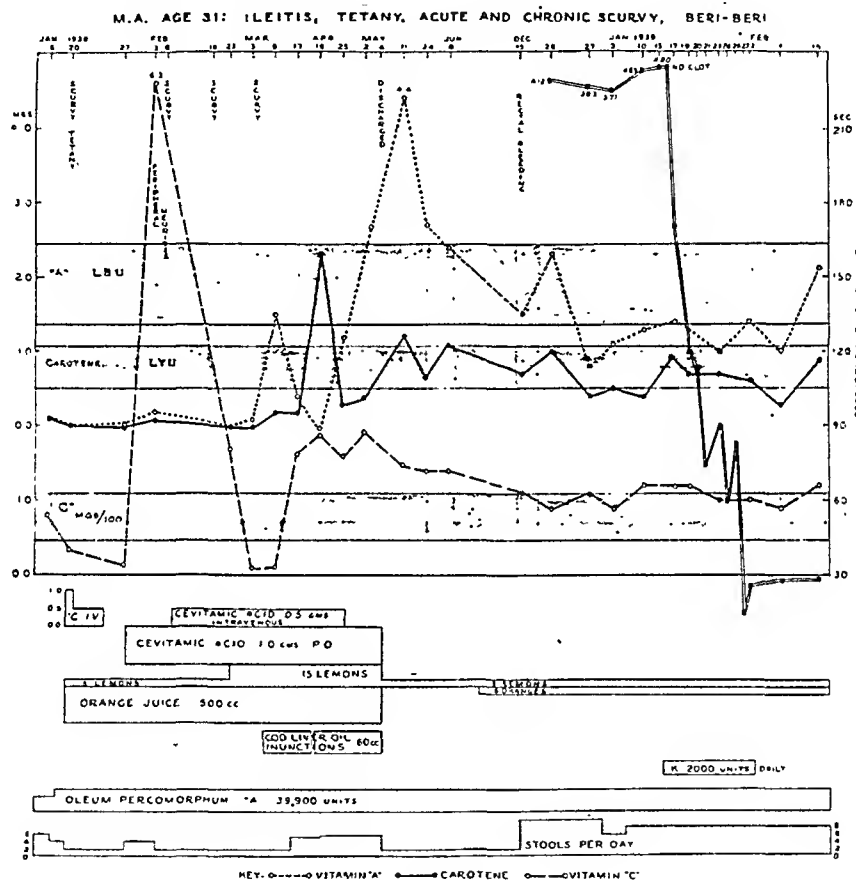
With the onset of the acute hemorrhagic episode the patient was given a transfusion of 750 cc. of citrated blood, and 1.0 gms. of cevitamic acid intravenously. Because of the gravity of his condition a blood Vitamin C determination could not be made until some hours later

anemia, and an acute hemorrhagic episode presenting the clinical phenomena of scurvy. Unfortunately it was not deemed wise to take blood for vitamin assay during the immediate post-operative period. The blood Vitamin "C" curve throughout the period of observation and the resumption of fruit juices within twelve hours of the operative procedure led us to believe that there was no danger of deficiency of this factor. It is unfortunate that a "C" determination could not be done prior to the transfusion and the intravenous administration of cevitamic acid. The observed value of 1.3 mgs. some hours later, however, does not suggest the existence of a "C" deficiency sufficiently severe to explain the clinical picture. It was of great interest to find the marked "K" deficiency in the absence of jaundice and likewise to observe the return of pro-

thrombin time to normal levels after the administration of 13 cc. of concentrate containing a total of 6,500 units of Vitamin "K." This was effective without the administration of bile salts. Although the cause of the hemorrhages cannot be stated positively in this instance, it seems probable that the "K" deficiency alone or in combination with a moderate deficit of "C" were responsible.

M. A.: The patient is a thirty year old Jewish male who was first seen on September 1, 1932. He gave a history of recurring attacks of chronic ulcerative colitis for three and a half years with recent recurrences. The history was irrelevant otherwise. Physical examination revealed nothing of note apart from proctoscopy which showed an acutely inflamed mucosa. Barium enema demonstrated a normal colon proximal to the sigmoid. Small in-

were no clinical indications of deficiency disease. Shortly thereafter small intestine X-rays revealed the characteristic changes seen in deficiency disease and suggestive evidence of new areas of regional enteritis. He was readmitted to hospital. In mid-December subacute glossitis appeared. There was a mild hypochromic anemia. The laboratory findings were suggestive of sprue. Consequently he was placed on a high protein low fat diet supplemented by large dosage of Vitamins A and D, and a rich source of B complex. There was no improvement on this regime and heavy parenteral dosage of liver extract had no apparent effect other than to correct the glossitis. Stools averaged from six to ten daily and from December 24th were controlled by opium and opium derivatives.



Graph 9

testine X-rays, however, suggested an organic lesion of the terminal ileum.

The colitis was brought under prompt control by dietary management and vaccine. There has been no recurrence.

In 1935 he began to have mild symptoms of intestinal obstruction and diarrhea. This condition became chronic. By February of 1937 the symptoms had developed to a point requiring hospitalization. A month later ileo-transverse colostomy was performed and subsequently resection of the diseased portion of the ileum and the proximal colon. The anatomic diagnosis was chronic non-specific enteritis. Convalescence was smooth.

In October of 1937 he returned complaining of increasing flatulence, distention and loose stools. The feces resembled those of sprue. The tongue was normal and there

On January 16th he complained of severe pain in the right gluteal region at the site of a previous liver extract injection. Examination revealed a large area of induration, increased heat, and extreme tenderness. Urinalysis at this time was negative.

The following day his condition was exceedingly grave. He was coughing and spitting considerable amounts of blood. There were large subcutaneous hemorrhages in the right upper arm. There was continuous oozing from a venipuncture in the ante-cubital fossa. The feces were tarry and contained bright blood. There was emesis of coffee ground material. He was unable to void and catheterization yielded grossly bloody urine. The hemoglobin had fallen to 32% (Sahli) and the erythrocyte count to 1,600,000. He complained of muscle cramps during the

morning and in the afternoon he developed a series of attacks of typical acute tetany. This acute episode was controlled by transfusion of 600 cc. of citrated blood, and by intravenous administration of 1.0 gm. of cevitamic acid and 60 cc. of 10% calcium gluconate solution.

For the next five days 0.5 gms. of cevitamic acid was given daily by vein. The fruit juices of the diet were permanently supplemented by 500 cc. of fresh orange juice and the juice of five lemons each day. By January 27th gross bleeding had ceased. The blood Vitamin C, however, was low and consequently 1.0 gm. of cevitamic acid by mouth daily was added and given continuously thereafter.

During the latter part of January the patient complained bitterly of increasing pain in all four extremities and of paresthesias of the hands and feet. By February 5th a frank peripheral neuritis of both arms and legs was evident, with marked motor weakness, muscle tenderness and diminished or absent deep reflexes. It was apparent that the clinical picture was further complicated by a classical beriberi. Consequently he was put on daily parenteral dosage of 3000 international units of thiamin.

February 6th cutaneous ecchymoses again appeared. Daily intravenous administration of 0.5 gms. of cevitamic acid was added. Two days later there was bleeding from the mouth and gums, ecchymoses and petechiae were scattered profusely over the entire body, and another attack of hematemesis occurred. Every hypodermic puncture was surrounded by an ecchymotic areola and slow continuous oozing of blood occurred from some. The hemoglobin was 44% (Sahli) and the erythrocyte count 1,900,000. A series of large transfusions were given.

On February 19th hemorrhagic areas reappeared in the buccal mucosa. A venipuncture oozed continuously for forty-eight hours. Four days later there was profuse bleeding from the gums and a newly-developed ulcer at the tip of the tongue. There were multiple subcutaneous hemorrhages and a large deep hemorrhage in the tissues of the left upper arm. The following day the Vitamin C sources were supplemented by the addition of the juice of ten lemons. This was continued up to the time of discharge. Slight bleeding from the gums continued intermittently. New bleeding areas developed on the base of the tongue, the floor of the mouth and the frenum.

During the first week in March he complained of pain in the left side of the neck. This was accompanied by swelling, induration and marked tenderness. Simultaneously a large submucosal hemorrhage appeared on the left side of the uvula and wall of the pharynx producing some respiratory obstruction and marked difficulty of deglutition. Bleeding ceased after March 7 and the patient made a slow but satisfactory convalescence. He was discharged on May 4th and has been followed at weekly or two weekly intervals in the Outpatient Department.

His subsequent course was uneventful until mid-December of 1938 when he began to pass considerable amounts of blood by rectum. Anoscopic, proctoscopic and X-ray examinations failed to reveal the source of bleeding. Repeated prothrombin determinations revealed no clot formation. There was no jaundice. Exhibition of Vitamin K 2000 units daily, kindly supplied by E. R. Squibb & Co., rapidly restored the prothrombin time to normal and diminished but did not entirely stop the bleeding. Bile salts were not administered with the "K" concentrate. (Graph 9).

VITAMIN ASSAYS

The first vitamin assay was done on January 6, 1938. The values for "A" and carotene were extremely low 0.1 LBU and 0.1 LYU respectively. The Vitamin C content 0.8 mgs. per 100 cc. was within the normal range. On January 20th, 3 days after the onset of acute scurvy and after 2.0 gms. of cevitamic acid intravenously in the preceding three days the Vitamin C level had fallen to 0.3 mgs. per 100 cc. and on the 27th to 0.14 mgs. per 100 cc.

despite the addition of 500 cc. of fresh orange juice and the juice of four lemons each day. The further addition of 1.0 gm. of cevitamic acid by mouth each day was followed by a rise to 6.3 mgs. per 100 cc. on February 3rd. On the 6th because of renewed bleeding half a gram of cevitamic acid each day intravenously was added to the schedule already in force. Withdrawal of blood for vitamin assay was not deemed advisable until February 23rd when the "C" content was 1.72 mgs. per 100 cc.

On the 24th the "C" sources were still further increased by the juice of ten additional lemons each day. On March 3rd and March 8th the blood "C" level remained at 0.1 mg. per 100 cc. coinciding with the final acute hemorrhagic episode. Throughout the remainder of the period of observation the blood "C" content remained within the normal range. Following discharge from the hospital the diet was supplemented by the juice of five lemons daily, and for most of the time by six oranges each day as well.

The blood Vitamin A level ranged from a trace to .2 LBU from January 6th through March 3rd despite the daily oral administration of 39,900 U.S.P. units of Vitamin A in the form of oleum percomorphum. From March 7th to May 4th with the exception of one day 60 cc. of cod liver oil were given daily by injection. There was an immediate rise and equally abrupt fall of the "A" curve followed by a sustained rise to 4.4 LBU on May 11th, a week following discharge from the hospital. Thereafter despite the continued oral administration of 39,900 units of Vitamin "A" in the form of oleum percomorphum the curve followed an irregular downward trend never, however, reaching the previous low levels.

The curve of blood carotene irregularly paralleled the Vitamin "A" curve.

The occurrence of rectal bleeding in December was not associated with an abnormal blood Vitamin "C" curve. Prothrombin determinations on six successive occasions showed complete failure of clot formation, the last on January 16, 1939. Vitamin "K" concentrate kindly supplied by E. R. Squibb & Co. was started on this date in daily dosage of 2000 units and continued through February 3rd. The prothrombin time dropped abruptly reaching 15 seconds on January 27th. There was no jaundice. The icterus index was normal. Bile salts were not administered with the "K" concentrate.

This patient must be regarded as a case of conditioned deficiency disease secondary to regional enteritis, presenting the characteristics of acute and chronic scurvy, acute tetany, acute beriberi, and nine months later acute Vitamin "K" deficiency in the absence of jaundice, with normal icterus index, and without other signs of hepatic disease.

SUMMARY

Accurate methods are now available for blood Vitamin C and K determinations. Although the technique and interpretation of Vitamin A estimations are open to criticism they are sufficiently accurate to have clinical value. Studies of a group of apparently healthy normal adults have been utilized to plot zones of apparent normality for Vitamins A, carotene, and C. Although the low limits found in the normal group cannot be accepted as the low limits of physiologic requirements, they constitute a useful basis for comparison. Our findings indicate that a significant proportion of healthy individuals taking average diets are well below the optimal level of blood Vitamin C. It is probable that certain of the A values are likewise low. The average Vitamin A and C values in a consecutive series of peptic ulcer cases are below the averages of the normal group, and the Vitamin C level is frequently very low. Similar deficiencies are not infre-

quent in chronic ulcerative colitis, and in the general ward population.

Repeated vitamin determinations have proved to be of inestimable value in the management of individual patients. They permit intelligent and controlled therapy of deficiency states. It is of interest that inunction of cod liver oil has proven to be an effective method of raising the blood Vitamin A level. It is likewise of interest to note that in certain severe deficiency states uncomplicated by jaundice a marked defect in prothrombin may occur associated with hemorrhage and responding promptly to the administration of Vitamin K concentrate without bile salts.

CONCLUSIONS

1. Subclinical vitamin deficiency states are not uncommon.
2. Methods of vitamin assay and normal standards are sufficiently accurate for clinical purposes.
3. Repeated vitamin assays frequently provide a most important guide to therapy.

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DISCUSSION

DR. HEINRICH NECHELES (Chicago): In view of the previous two papers, I should like to point out the importance of the factor of absorption in the gastro-intestinal tract, which seems to be overlooked by a number of investigators. If vitamins are given by mouth and cannot be absorbed, it is as good as if they are not given. We have seen that in patients and animals, and I very much feel that the ultimate way out will be to have most vitamins in soluble preparations for injections.

In all cases of atrophy or inflammation of the gastro-intestinal mucosa, or of diarrhea, administration by mouth, even of huge doses, may be useless.

Another point I want to make is that although it is believed that single, isolated vitamins are specific for certain clinical conditions, it becomes more and more evident that we have to administer groups of vitamins, and that seems to be quite evident from previous papers. For instance, the conviction is growing in many observers that in pellagra, it is not nicotinic acid alone, which ultimately cures, but a combination of several factors of the B group.

To give yeast is pretty useless in a number of patients because yeast is hydrolyzed with difficulty. In the absence of essential ferments, especially of trypsin, the yeast is utilized little or not at all, and it would be very good if yeast would be eliminated entirely from cases that have a disturbance in their digestive canal and an injectible yeast extract used instead.

Clinical Observations on the Possible Relationship of Digestive Tract Disease to a Type of Osteoporosis*

By

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and

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WITH the advancement in knowledge of nutritional and endocrine disorders and development in roentgenological and chemical methods more attention has been called to disorders of mineral metabolism. Generalized demineralization of bone is observed to a striking degree in hyperparathyroidism, further characterized by a high serum calcium and low serum phosphorus. Numerous reports in the literature (1, 2, 3) mention association of osteoporosis in some instances of long standing hyperthyroidism, the exact mechanism by which this occurs being rather uncertain or obscure, but indicative of the more extensive alteration of the metabolic physiology in this disease. Generalized demineralization of bone has been

observed in cases of long standing nephritis (4, 5) referred to as hyperparathyroidism secondary to renal functional impairment, and related to the retention of phosphates because of the inability of the kidney to excrete them adequately. Chronic steatorrhea may be accompanied by osteoporosis, probably due to excessive loss of calcium in the feces (6, 7). Poorly balanced or deficient nutrition may be important in the production of osteoporosis. A recent editorial in the *Journal of the American Medical Association* on senile osteoporosis (8) relates that the "theory that protracted deficiencies in basic nutrition resulting from poor dietary habits may impair the health of the adult and contribute to the factors which produce disabilities commonly attributed to 'old age' has rarely been postulated," and calls attention accordingly that "gradual demineralization of the skeleton over a

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period of years may result in pathologic changes in the kidneys or other vital organs and hence affect unfavorably the health of the patient." Furthermore, it is stated that "generalized osteoporosis in the adult can be explained only on a basis of chronic or intermittent negative mineral balance over a period of many years."

Deminerization of the skeleton represents an important degree of depletion of storage of calcium and indicates an inadequate absorption or an increased excretion of calcium over a long period. Apparently the physiologic process is able to maintain a surprisingly constant level of the transport calcium, and for this reason cases of osteoporosis may be free from symptoms due to hypocalcemia or hyperealcemia. Calcium absorption may be increased (9) by a high calcium diet, cod liver oil (Vitamin D), increased intestinal acidity by converting insoluble phosphate into soluble compounds of calcium, and systemic acidosis; and calcium absorption may be decreased by diarrhea, a low calcium diet, a high phosphorus diet, poor utilization of fat and fatty acid, and alkalinity of the intestinal contents.

TABLE I

Age	G. I. Symptoms		No G I Symptoms		Total
	Male	Female	Male	Female	
Under 30	0	0	1	0	1
30-39	0	1	0	1	2
40-49	0	3	0	0	3
50-59	1	6	0	5	12
60-69	1	6	2	16	10
70-79	2	2	2	6	12
80 or over	0	0	0	1	1
Sub-total	4	18	5	23	50
Total	22		28		50

In support of the view that absorption of calcium is decreased by insufficient acid reaction of the contents of the upper small intestine, Bussabarger, Freeman and Ivy produced severe homogeneous osteoporosis by gastrectomy in puppies (10). Osteoporosis might be expected in achlorhydria of long standing.

Occasional severe generalized osteoporosis is encountered in the adult in an age before senility, and unaccompanied by the change in blood chemistry characteristic of hyperparathyroidism. Such patients often complain of generalized aches and pains and weakness and not infrequently have vague gastro-intestinal symptoms. As the age of 60 is approached it is often difficult to separate such cases from so-called senile osteoporosis, but it can be said that such osteoporosis may exist without other characteristics of senility.

Fifty cases of generalized osteoporosis were selected for study. None of these cases had the characteristic changes in blood chemistry of hyperparathyroidism. Undoubtedly some of the cases of older age were cases of senile osteoporosis, but there was a sufficient number under the age of 60 without other evidences

of senility to be significant for the purposes of this study. All of these cases had a sufficient degree of osteoporosis to be easily recognized from the roentgenograms. A standard technique in taking films and extreme caution is necessary to avoid error in interpretation of the presence or absence of osteoporosis. It has been estimated that in decalcification the calcium loss must be from 20% to 40% in order to be

TABLE II

Gastro-intestinal symptoms in twenty-two cases of osteoporosis

Symptom	No. of Cases
Anorexia	9
Nausea	10
Vomiting	7
Vague abdominal pain	8
Diarrhea	1
Constipation	16
Indigestion, Vague, unqualified	9
Sensation of fullness in abdomen	8

visible by X-ray (11). Therefore, these cases represent severe osteoporosis. The difficulty in recognizing lesser degrees of osteoporosis may account for the many diagnoses of neurosis or other functional disturbance so long before the true mineral metabolic disorder is discovered.

Of these 50 patients 22 or 44% had gastro-intestinal symptoms. Since we are interested here particularly in those with gastro-intestinal symptoms the other 28 are not included in this report other than to correlate their age and sex incidence which is demonstrated in Table I.

Of the cases with gastro-intestinal systems 18 or 82% were female and 4 or 18% were male. The ages range from 34 years to 71 years; eleven or 50% were under 60 years of age, and in this group there were 10 females and 1 male. In the group over 60 years of age there were 8 females and 3 males. The sex and age incidence was fairly comparable to that of the group in which there were no gastro-intestinal symptoms.

TABLE III

Duration of G. I. symptoms range from 1 month to 20 years

1 year or under	9
1-5 years	3
5-10 years	5
10-20 years	5
Total	22

The gastro-intestinal symptoms in order of their frequency were: constipation; nausea; vague, unqualified indigestion; anorexia; vague abdominal pains; sensation of fullness in the abdomen, and occasional vomiting.

In the cases of long duration the symptoms were variable but some time during the history several of these symptoms were present alone or in combination.

The gastro-intestinal symptoms ranged in duration 1 month to 20 years, the majority having symptoms over 1 year and nearly one-half of the cases had symptoms over 5 years.

Organic digestive tract disease was demonstrated in 11 or 50% of the cases and for this reason it is difficult to evaluate the origin or significance of the gastro-intestinal symptoms. The diagnoses of the organic conditions are listed in Table IV.

TABLE IV

Organic digestive tract disease in 22 cases of osteoporosis having gastro-intestinal symptoms

Chronic Cholecystitis without stones.....	3
Chronic Cholecystitis with stones.....	1
Duodenal ulcer.....	1
Chronic esophageal ulcer.....	1
Carcinoma colon.....	1
Carcinoma rectum.....	1
Diabetes mellitus.....	3
Total.....	11

The four cases of gall bladder disease were proven at operation. The duodenal ulcer was proven by X-ray and was accompanied by a typical hyperacidity curve. The esophageal ulcer was demonstrated by X-ray and esophagoscope, and malignancy has been ruled out by healing with stricture and long duration of life. The two cases of carcinoma of the lower bowel had symptoms referable to the local lesions only a short time and it seems reasonable that other very chronic gastro-intestinal symptoms were on some other basis. It is doubtful whether any gastro-intestinal symptoms should be attributed to the diabetes in the three cases included.

Further analytical breaking up of the remaining group of 11 cases without demonstrable organic digestive tract disease shows 6 cases under 60 years of age, and seemingly justifiably classed as non-senile, in

TABLE V

6 cases under 60 years age with G. I. symptoms and no demonstrated organic digestive tract disease

Age	Sex	Duration of Symptoms
34	F.	2 years
59	F.	1 year
58	F.	6 years
58	M.	20 years
43	F.	18 years
51	F.	20 years

whom there were gastro-intestinal symptoms. This group is particularly important in attempting to appraise an association of gastro-intestinal symptoms with generalized osteoporosis. Age and sex incidence and duration of symptoms of this group are given in Table V.

A careful review of the symptomatology of these 6 cases shows them all very similar in character. Anorexia, feeling of fullness in the abdomen with or

without gaseous eructation, vague abdominal pains, vague unqualified indigestion, nausea with occasional vomiting, and constipation were complaints in all cases, and these symptoms seemed to vary somewhat from time to time.

Chronic cholecystitis, irritable colon or spastic constipation, and gastric neurosis were tentative diagnoses offered at some time or other in the course of these cases before the osteoporosis was discovered. Available dietary history did not reveal any definite tendency to taking of a calcium deficient diet, but it was interesting that almost universally there was a suggestion of intolerance of fatty foods. However, there was a suggestion of either insufficient calcium intake or inefficient absorption of calcium in two cases which responded symptomatically to the administration of 6 grams of diacalcium phosphate with viosterol (3600 units U.S.P.) daily, showing measurable replacement of calcium in the skeleton within two to three weeks as determined by a standardization method developed by Dr. George C. Henny of the Department of Radiology to be reported elsewhere. How complete and permanent such therapy will be in replacing calcium and ameliorating symptoms remains to be seen, and, of course, caution should be urged in

TABLE VI

Case No.	Blood Calcium	Blood Phosphorus	Blood Phosphatase
3	10.7	2.96	2.52
7	9.0	3.4	
8	11.0	2.0	
11	10.3	3.6	
15	10.0	3.9	7.0
18	11.8	4.6	
21	9.6	3.3	
23	12.9	7.9	
24	9.1	4.4	1.4
25	9.5	4.5	4.0

interpreting the gastro-intestinal symptoms as due to calcium deficiency.

Blood serum calcium and phosphorus were determined in 10 of the cases having gastro-intestinal symptoms, and phosphatase was determined in 4 cases. These are given in Table VI, and show essentially normal values except in one case in which both calcium and phosphorus were somewhat elevated, and in another case the phosphatase was slightly elevated. In 5 of the 6 cases under 60 years of age having gastro-intestinal symptoms without demonstrable organic digestive tract disease, blood serum calcium and phosphorus determinations were available and all within normal limits.

Gastric analyses were not available, so the question of whether gastric acidity might be etiological could not be answered. However, 19 cases of pernicious anemia, all with gastric analysis and the characteristic acidity, were studied for generalized osteoporosis and only 1 case showed it to be present.

As further controls, 50 recent cases of chronic cholecystitis as diagnosed by clinical history and physical examination, and non-functioning gall bladder

by X-ray (oral method) were studied, several of these being confirmed by operation, and only 1 case of generalized osteoporosis was found. Also 23 cases of chronic colitis of long standing were studied and no cases of generalized osteoporosis found.

SUMMARY AND COMMENT

Fifty cases of generalized osteoporosis in the adult were studied and 22 were found to have gastro-intestinal symptoms. None of these cases had the changes in blood chemistry of hyperparathyroidism. It is obvious, therefore, that severe generalized osteoporosis may be and often is without gastro-intestinal symptoms. This type of osteoporosis, with or without gastro-intestinal symptoms, is predominant in the female. Some of the cases were necessarily considered to be senile osteoporosis because of the age. There was no obvious cause of the osteoporosis, such as long standing hyperthyroidism, chronic steatorrhea, or chronic diarrhea. When organic digestive tract disease was present in those cases having gastro-intestinal tract symptoms, chronic cholecystitis was the most common diagnosis. A careful review of 6 cases under the age of 60 having gastro-intestinal symptoms but no demonstrable organic digestive tract disease, showed a marked predominance of females, the duration of the symptoms generally to be a number of years, and the gastro-intestinal symptoms consisted of anorexia, feeling of fullness in the abdomen, with or without gaseous eructation, vague abdominal pains, vague unqualified indigestion, nausea with occasional vomiting, and constipation. It seems likely these gastro-intestinal symptoms are not caused by osteoporosis, but rather that patients, particularly women from 45 to 60 years of age, having such symptoms of long duration may have some nutritional deficiency or disorder of calcium absorption resulting in chronic or intermittent negative mineral balance. Calcium balance studies in well selected cases, to be reported later, should add to our understanding of this type of osteoporosis.

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DISCUSSION

DR. JOHN L. KANTOR (New York): I should like to take this opportunity to discuss several papers together,

Dr. Althausen's yesterday, Dr. Wilbur's this morning, Dr. Mackie's and Dr. Brown's.

I think we are now in a position to look at this subject in a broad way. In my opinion, it is not so important to stress the fact that we are dealing with a deficiency disease here as it is to emphasize that we have a failure of absorption. It isn't that these patients haven't been getting vitamins but they are "funny" kind of people, who cannot absorb vitamins, and I think Dr. Mackie's chart confirms this thought. He didn't show much difference in absorptive power between the ulcerative colitis group, the ulcer group, and miscellaneous ward patients.

One can get at this inability from X-ray studies such as Dr. Mackie and others have done, or from a study of the fat in the stools. It is the fat that is the hardest thing to absorb and the easiest to pick up, provided tests are available. Unfortunately, these tests are not done in most institutions, at least on a quantitative basis.

(Dr. Kantor then showed a series of slides illustrating the roentgen diagnosis of idiopathic steatorrhea. The chief changes were in the small intestine where the mucosal pattern showed a loss of the valvulae conniventes (so-called "moulage sign") and there was segmental dilatation and occlusive spasm).

DR. ANDREW C. IVY (Chicago): I should like to ask Dr. Brown if he studied the rate of gastric emptying in any of the patients. The results we reported from our laboratory on the occurrence of homogeneous osteoporosis in gastrectomized animals were due to an acidity plus other factors. These animals had lost the reservoir function of their stomach, and the food was rapidly passed through the upper part of the intestine where normally most of the calcium is absorbed; so if a patient has achlorhydria plus a rapidly emptying or a dumping stomach, the presence of the two factors would be more likely to produce a disturbance of calcium metabolism than achlorhydria alone.

Another factor we need to keep in mind is that achlorhydric patients tend to manifest a post-cibal acidosis, because while they are not secreting acid in the stomach, they are secreting alkaline bile and pancreatic juice which obviously tends to produce an acidosis; and presence of an acidosis when calcium is being absorbed, tends to decrease calcium retention. It is generally known, one can decalcify bone by maintaining an acidosis over a long period of time.

I might add that we have seen a patient with homogeneous osteoporosis and multiple fractures which resulted three years after a radical gastric resection.

DR. THEODORE L. ALTHAUSEN (San Francisco): Our experimental work on the intestinal exchange of calcium in rats supports the findings of Drs. Brown and Vogel. In attempting to discover the cause of the negative calcium balance in patients with hyperthyroidism, which in severe cases may end in osteoporosis, we found that the intestinal absorption and excretion of calcium were normal in hyperthyroid rats. Since the fecal output of calcium is approximately doubled in hyperthyroid rats, we conceived the idea that increased intestinal motility may be an important factor. This was shown to be correct when administration of castor oil or of cascara in very small doses, insufficient to produce diarrhea in any of the animals, resulted in twice the normal output of calcium in the feces of normal rats fed a calcium-free diet. Conversely, administration of morphine to slow intestinal peristalsis reduced the fecal calcium of hyperthyroid rats almost to normal.

Our findings not only explain the existence of a negative calcium balance in hyperthyroidism in spite of a normal blood calcium level, but also explain the lack of loss of calcium through the feces in patients with hyperpara-

thyroidism who do have an increased level of calcium in the blood.

Meulengracht recently described the occurrence of osteomalacia of the spine due to chronic misuse of cathartics.

DR. CHARLES L. BROWN (Philadelphia): I have no comment to make in closing. In answer to Dr. Ivy's question, two of these cases did show what might be considered as an increased rapidity of emptying of the stomach.

The Role of the Circulation in the Production of Peptic Ulcer

By

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and

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ALTHOUGH no single etiologic factor has been established as the cause of peptic ulcer, analysis of conditions under which ulcer occurs, suggests that the local lesion is mediated through alterations in circulatory efficiency. Such alterations may be mechanical or quantitative as in cardiovascular disease, nutritional or qualitative as in metabolic disturbances, anaemia, blood dyscrasia and infections, or functional or vasomotor as the result of disturbances in the sympathetic nervous system. But regardless of the mode of production of the circulatory insufficiency, the ulcer is the result of local alteration of nutrition of the stomach wall.

The anatomic peculiarities of the vascular bed of the stomach (1) and its rich vasomotor innervation, predispose this viscus to local deficiencies in blood supply. However the production of gastric ulcer by experimental blood protein depletion or plasmapheresis (2) and by repeated injections of pitressin, (3) suggests that the gastric ulcer is not necessarily an isolated nutritional disturbance of the stomach wall, but part of a generalized circulatory insufficiency intensified in focal areas of the stomach because of the anatomic structure of its intrinsic circulatory bed and its neural peculiarities.

With the purpose of evaluating the role of circulatory insufficiency in the mechanism of gastric ulcer, we have analyzed a series of 161 cases which at post mortem presented acute lesions of the gastric mucosa. These cases represent a cross section of the autopsy material of a general hospital. Although the cause of death varied widely, the cases can be divided into four primary categories.

CHART I

Etiologic factors in acute lesions of the gastric mucosa

161 Cases	
Cardiovascular disease	77
Metabolic disturbances	52
Primary cerebral disease	18
Anaemia, blood dyscrasia, and chronic infection	14

CHART II

Etiologic factors in acute lesions of the gastric mucosa—cardio-vascular disease (quantitative circulatory insufficiency)

77 Cases	
Hypertensive cardio-vascular renal disease	27
Chronic myocardial degeneration	23
Essential hypertension	11
Chronic rheumatic valvulitis	10
Syphilitic cardio-vascular disease	4
Congenital heart disease	2

CHART III

Etiologic factors in acute lesions of the gastric mucosa—metabolic disturbances (qualitative circulatory insufficiency)

52 Cases	
Hepatic insufficiency	23
B ₁ avitaminosis (1)	14
Diabetes mellitus	8
Chronic metallic poisoning (2)	7

(1)—Chronic alcoholism 10, chronic vomiting 4; (2)—Lead poisoning 6, arsenic poisoning 1.

CHART IV

Etiologic factors in acute lesions of the gastric mucosa—primary cerebral disease (vaso-motor circulatory insufficiency)

18 Cases	
Expanding intracranial lesions (1)	13
General paresis of the insane	2
Multiple sclerosis	2
Chronic traumatic encephalopathy	1

(1)—Primary cerebral abscess 3, brain tumor 10.

CHART V

Etiologic factors in acute lesions of the gastric mucosa—anaemia, blood dyscrasia and chronic infection (qualitative circulatory insufficiency)

14 Cases	
Secondary anaemia	9
Chronic infection (1)	4
Blood dyscrasia (2)	1

(1)—Lung abscess 2, empyema 1, pulmonary tb. 1; (2)—Hemorrhagic disease of the new born 1.

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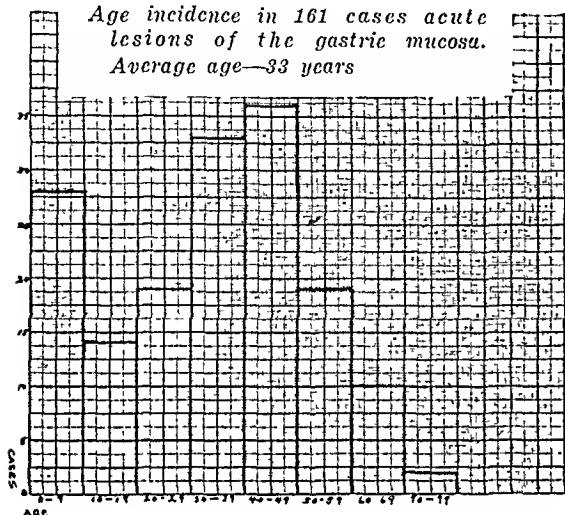
The Philadelphia General Hospital, Philadelphia, Pa.

Read at the Annual 1935 Session of the American Gastro-Enterological Association at Atlantic City.

In order to facilitate comparison with clinical cases of ulcer, and to minimize the cardiovascular insufficiency of older age groups we have chosen our cases predominantly from the younger age levels. The frequency table shows fair agreement with that of the incidence of clinical cases of ulcer. The average was 33 years, and 80% of the cases were under 50 years of age.

TABLE I

*Age incidence in 161 cases acute lesions of the gastric mucosa.
Average age—33 years*



The following types of acute lesions of the gastric mucosa were found in this series.

CHART VI
Acute lesions gastric mucosa
161 Cases

Type	Cases	Per Cent
Perforations	16	10
Mucosal hemorrhages	25	16
Macroscopic ulcers	41	24
Microscopic ulcers	40	25
Microscopic erosions	16	10
Severe congestion	23	14

Although the lesions of the gastric mucosa were acute, histologic study, using differential stains demonstrated that in the area of the mucosal lesion all the layers of the stomach wall were involved. Further, although the mucosal degenerations were acute, the alterations in the deeper layers were essentially chronic. In no area examined was the mucosa alone involved. The mucosal alterations were invariably superimposed upon chronically degenerated submucosal and muscular layers. Conversely, it was possible to demonstrate areas adjacent to the acute mucosal lesions where normal healthy mucosa had regenerated despite chronic alterations in the deeper layers.

The wedge shaped pattern in the acute mucosal lesion and the picture of chronic alteration in the deeper layers suggests that vascular deficiency of a



Fig. 1. Focal erosion (ischemic necrosis) of distal portion gastric mucosa. Fibrosis muscularis mucosae. Varicose dilatation of vessels of submucosa due to chronic stasis. Atrophy and fibrosis muscular coat.

persistent or recurrent type had existed. The muscle coats were oedematous, decreased in thickness and showed metamorphic basophilic staining with the trichrome stain. There was marked proliferation of connective tissue reticulum between both the individual muscle fibres and the circular and longitudinal coats. In the submucosa, with its vascular plexes, the evidence of prolonged stasis was most marked. The veins were tortuous, almost to the point of varicosity, while both veins and arteries showed fibrosis of the walls. The entire coat was increased in width, and its loose areolar structure was replaced by dense, structureless hyalin material, or in many cases, by fibrous connective tissue. This resulted in a fusion of the layers of the stomach wall. In practically all cases the muscularis mucosa had been replaced by connective tissue which showed focal proliferation at the base of the mucosa and extended along the trabeculae between the gastric glands. Thus, although the mucosa has no independent blood supply, histologic study showed that



Fig. 2. Focal ulcer involving entire depth of mucosal layer (ischemic necrosis). Fibrosis of deeper structure with atrophy of muscular coat.



Fig. 3. Necrosis and desquamation of mucosa at right (acute ulcer). Varicose dilatation of submucosal vessels. Muscular layer replaced by connective tissue except for small area at extreme right.

normal or acutely altered mucosa may be present when the deeper structures, which are closer to the stem artery, show the effects of prolonged or repeated periods of circulatory stasis.

The apparent paradox can be explained by the fact that regeneration of the mucosal coat following repeated focal destruction can occur at the same time that progressive degenerative changes are taking place in the deeper structures which possess less potentiality of regeneration.

In order to present the relative changes in the entire thickness of the gastric wall, we have utilized microscopic-sized mucosal lesions for our illustrations. However, it is possible to reconstruct the same progress of events in the acute macroscopic ulcers.*

*The trichrome stain used to demonstrate the sections is original with Miss Edna Beyer, technical assistant in the division of neuropathology of the Philadelphia General Hospital. Connective tissue, collagen and mucus stain blue, while gastric glands stain red. Muscle in its normal state takes the red stain, but becomes increasingly basophilic as degeneration progresses. To be published in *Am. J. Clin. Path.*



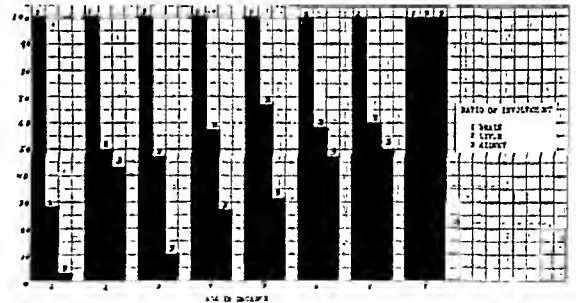
Fig. 4. Hyalinization of submucosal layer. Atrophic changes in muscular coat. Mucosa is atrophic and shows focal ischemic degeneration at one point. Complete fusion of all coats. This is probably an irreversible stage.

Although the nature of these gastric lesions strongly suggests an insufficiency of the circulation, study of the stomach lesion itself gives no clue whether this condition is a local one or due to general insufficiency with its frequently resulting widespread stasis. For this reason, using the same criteria employed in the histologic study of the gastric lesion, namely degeneration of parenchymatous cells with proliferation of connective tissue, we attempted an evaluation of the presence of generalized circulatory insufficiency by examining the brain, liver and kidney in those cases presenting acute lesions of the gastric mucosa. The evidence of impaired circulation found in these organs would make it reasonable to assume that the anatomically inadequate blood supply and the intrinsic vasomotor innervation of the stomach do not cause the gastric lesion through local disturbances alone, but merely intensify a local picture incident to the generalized insufficiency of the circulation.

As might be expected, the brain with its functional dependence upon the integrity of the systemic circulation showed the earliest reflection of generalized circulatory insufficiency. In 37% of the series, it was the only organ, except the stomach to show degenerative changes. On the other hand, there was no case with a gastric lesion which did not show brain involvement as well. The liver, with the same blood supply as the stomach, was involved in only 53% of the cases. Lesions incident to chronic stasis were present in the kidneys in 38%. The graph demonstrates that the ratio of brain, liver, kidney involvement increases with age.

TABLE II

General circulatory insufficiency in 161 cases of acute lesions of the gastric mucosa



CONCLUSION

From histologic study of 161 cases of acute focal lesions of the gastric mucosa, we would conclude.

1. Regardless of etiology, focal gastric lesions are the result of chronic circulatory insufficiency to all the structures of the gastric wall.
2. Such circulatory deficiency is part of a generalized insufficiency intensified by intrinsic vascular peculiarities of the stomach, of an anatomical or vasomotor nature.
3. Generalized circulatory insufficiency may be established through quantitative, qualitative or vasomotor alterations in the circulatory system.

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DISCUSSION

DR. CHARLES M. WILHELMJ (Omaha): I want to congratulate Dr. Boles and his colleagues for this very important and very intriguing study.

The facts, I think, were clear enough from their slides. Of course, what is back of these changes is open to speculation. I should like to point out that a similar acute vascular lesion is found very often in dogs under a variety of conditions. For instance, we find that in animals dying from distemper, adrenal insufficiency, obstructive jaundice, or total biliary fistula, these types of changes are very likely to occur, as a matter of fact, almost always. I have also seen similar lesions in animals dying from foreign protein shock.

It is well known among physiologists, at least, that if the causative factor is removed, all of these acute mucosal hemorrhagic vascular lesions will heal and heal quite promptly; for instance, if the biliary obstruction is relieved, or there is removal of the total biliary fistula, they will clear up, but if the causative agent continues to exert its influence, many of these acute lesions will go on to chronic lesions such as we see in total biliary fistula, obstructive jaundice, and other conditions.

I think that in the present work there are two very important findings: First, the evidence of repeated insults. These were not acute, as you saw from the degenerative change or changes going on in the deeper layers, where the muscular layers have been almost completely replaced by fibrous tissue, so these things were coming repeatedly, which gives us one of the factors which may lead to chronicity.

The second thing which I think is of importance is the fact that they found similar lesions in the brain and the liver, lesions at least that suggested that the same changes were going on.

Now, that the nervous system may be involved in the production of chronic ulcer is more or less generally accepted, although it is very hard to prove it experimentally.

Of course, the lesions which have been pointed out by Cushing and by others, and also the experimental lesions produced after hypothalamic injury, suggest that the nervous system is involved. The essayists also told me they had found pathological changes in the vagus nerves and the sympathetic ganglia.

The changes in the liver, I think, are very important. I am coming more and more to the belief that the liver may be a very important factor in the genesis of chronic peptic ulcer. It is a difficult thing to prove, but more and more evidence is pointing to the liver as one of the important factors.

They found lesions in the liver, so that they have here three things which you might expect finally to lead to chronic ulcers in certain of these patients:

- (1) Repeated insults, not just one, but repeated.
- (2) The nervous system was involved, which might lead eventually to hyper-secretion, spasm, and so forth.
- (3) The liver was involved, which might bring in what I personally believe to be an important but, at the present time, an unknown factor. I wish to congratulate Dr. Boles and his colleagues upon this very significant work.

DR. RUDOLF SCHINDLER (Chicago): May I ask one question, Dr. Riggs? How did you differentiate these acute lesions you saw in autopsy material, from the well known postmortem changes? I could not get this point.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): Any contribution that may throw light on the genesis of acute and chronic gastric ulcer is certainly welcomed by this Society. I am of the opinion that the acute lesion is frequently the basis for gross bleeding without any other

manifestations. I hope that the essayist will describe the technic of tissue staining, as the slides which they have shown are beautiful in this respect. I think that Doctor Necheles will agree with me.

Doctor Necheles: Yes.

Doctor Eusterman: We may also have to revise our conception of the gross pathology of chronic gastric ulcer in view of this report, because the older school has taught that an ulcer is only chronic when it reaches the depth of the muscular layer or serosa. The ability of the mucosa to thoroughly regenerate itself is a well established fact, as is borne out by pathologic studies for years past on healed acute and chronic gastric ulcer.

I am curious to know if the lesions under discussion give rise to any symptoms during the life of the individual. To what extent such acute lesions can give rise to lesions other than gross and occult bleeding, and their causative relation to chronic ulcer, is not yet clear. In recent years the thought has been advanced in sundry parts of the scientific world that we must forget about acute ulcer being the precursor of a chronic one before we can learn anything etiologically about the latter. The causative role of vascular nature is refuted by many pathologists, notably Aschoff, although we know that to vascular spasm von Bergmann attributes fundamental importance. Finally, I wish to state that while chronic ulcers are frequently seen in association with disease of the central nervous, cardiovascular, renal and endocrine systems, which may or may not give rise to very marked disturbances, such lesions in association with disease of the biliary tract are much less frequent than one would expect. At least from my clinical experience, the relationship of hepatic disease to the genesis of ulcer appears to be a very doubtful one.

DR. ANDREW C. IVY (Chicago): Some have suggested that they believe the cause of these acute lesions is vomiting prior to death; that is, the spasm of the pyloric antrum causes a rupture of the blood vessels, hemorrhage into the mucosa which is followed by digestion. This mechanism can cause acute ulcers in animals in the laboratory; it is very easily demonstrated; but vomiting and pylorospasm has not been proven to be a cause of acute lesions in the stomach of man.

I believe that the essayists could make a contribution, since they observe a difference in the distribution of acute lesions depending on the cause of death, by going into the history of their patients and ascertaining if they vomited prior to death.

I noted that cardiac insufficiency heads the list as a possible related cause of these acute lesions. We frequently administer digitalis to such patients, and we know digitalis is a gastric irritant and causes vomiting.

DR. HEINRICH NECHELES (Chicago): I am particularly happy about this paper because I feel that it confirms some of the results reported yesterday by Dr. Schindler and myself. About 15 years ago Mueller and Heimberger showed that in all ulcer patients whom they examined, tortuous capillaries were present in the skin, the lips and in the gastric mucosa; this was such an amazing finding that I was surprised that it never had been repeated, and wanted to do it myself. I am particularly happy to see that Dr. Boles has been able to attack this question from quite another angle, and much more profoundly than Mueller.

The old question whether ulcer is due to local or to general disturbances, is brought nearer to a solution by Dr. Boles' work, which points definitely to generalized disturbances in circulation in ulcer patients.

You may not have read a recent paper by Dr. Babkin in which he proposes that histamine may play a rôle in the formation of ulcer. We have proposed that acetylcholine

plays a rôle. Both theories assume disturbances in the vascular supply of the stomach, especially in areas with end vessels, where there are few or no collaterals, areas which are much more prone to devitalization in case of spasm or of stasis; and these regions show the greatest incidence of ulcers; namely, the lesser curvature and the duodenal bulb.

It is, of course, a very difficult question to decide whether these numerous and rather general pathological findings are coincidental with ulcer or causal to ulcer.

One thing impressed me very much, and that is the very distinct appearance of stasis and tortuosity of the capillaries, and I think the beautiful technic, on which I want to congratulate Dr. Riggs, brings that out most clearly.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): Twenty-five years ago and for many years thereafter, one of our members, Fenton B. Turck, presented to this Association reports of his observations on the production of stomach ulcers in animals, during the course of his experiments on shock. Extracts of dead tissue of the animals were injected intravenously into the same or other animals of the same species, producing all the manifestations of shock, including the focal necrosis in various organs, such as brain, liver and stomach. He pointed out that when these lesions occurred in the stomach they were pathologically identical with those of lesions which we had been calling chronic gastric ulcers, even though it had taken only a matter of minutes to produce them. He called the factor producing shock and these lesions at first shock toxin, then cytolsin and finally cytost. At one of our meetings I pointed out that such a factor would be present in the dead tissue occurring at the site of a so-called focal infection and might account for the relationship between such infections and peptic ulcers. Later, Lewis Gregory Cole presented to us his proofs that peptic ulcers are acute, and that, barring complications, they heal rapidly, often leaving scars so fine as to be recognizable only microscopically. Pathologists have called attention to the frequent finding at autopsies of multiple healed lesions which must have been peptic ulcers.

My conception of an ulcer is that it is an acute process, healing rapidly and spontaneously, and not becoming chronic unless its base has penetrated or almost penetrated the serosa, producing marked infiltration of the wall and perigastric or periduodenal adhesions and induration. The lesion then becomes a chronic process, producing deformities and physiological disturbances usually requiring surgical intervention.

My feeling is that this report of Dr. Boles and his associates is one of the most important events of this meeting. Dr. Boles has again scored by reporting on pathological material, of which we are getting too little these days. His findings, in my opinion, constitute another step in the confirmation of the theories of Turck and Cole.

DR. RUSSELL S. BOLES (Philadelphia): Mr. President, I want to express the very deep appreciation of Dr. Riggs, Dr. Griffiths, and myself, for this very generous discussion.

I wish I had time to answer all the discussers in detail, but I will have to refer briefly to their questions and, if there is anything further I shall be glad to see them later.

Dr. Schandler asked how the histologic picture differs

from that of acute focal post-mortem necrosis. I think the stain speaks for itself in this respect. Certainly the chronic changes noted in the deeper layers are not the result of post-mortem degeneration. These same changes were observed by Nedzel in his experimental work in dogs.

Dr. Eusterman asked if the patients had any symptoms of ulcer. We have not completed a clinical survey of the cases and hope to do this later. We can say at this time that most of the patients did not present the conventional symptoms of chronic peptic ulcer.

In answer to Dr. Ivy's question, I might say that less than 10 per cent had any history of vomiting.

Dr. Andresen mentioned that an ulcer doesn't become chronic except under certain circumstances. We believe that it does not become chronic until there is absolute incapacity of the mucosa to regenerate itself because of the chronic degenerative changes in the deeper layers that we have demonstrated.

This paper, for me, holds considerable interest because of the clinical implications that may be derived from it. To begin with, I think it is becoming increasingly obvious that the solution of this question of peptic ulcer depends quite definitely on a broad, general approach to it. This is particularly important in formulating an intelligent method for the medical and especially the surgical management of the disease.

"Peptic ulcer," unfortunately to me is a very unscientific and misleading term to use to designate this disease. We must get a different name for it because the term "peptic ulcer" concentrates attention primarily on a local lesion in the stomach. We wouldn't think of doing this, for instance, in diabetes. We don't concentrate our attention on the ulcer of the toe in diabetes, or in Buerger's disease, or in arteriosclerosis or in other conditions in which an ulcer is simply an end result.

Another thing that impresses me as a result of this study is the possibility that there may be a common denominator not only in peptic ulcer disease, as I like to think of it, but in such similar conditions as coronary artery disease, and thrombo-angiitis obliterans, or Buerger's disease; in other words, in diseases of the peripheral or end-arteries in various other structures.

The approach, then, I think, as I said before, must certainly be from a broad, general point of view. We must stop studying ulcer as a local lesion. We must begin wondering about the serum proteins. Why does a patient with ulcer have a high hemoglobin and red cell count? What is the viscosity of the blood? Why is it increased, as it invariably is in Buerger's disease, for instance. The symptoms and many of the sequences of events clinically and pathologically are similar in the two conditions. The nervous symptoms in peptic ulcer disease we suspect may be due to the vascular stasis that occurs in the brain and the neural structures.

That the circulatory factor in ulcer are important is suggested by the effect on the lesion of certain drugs—tobacco for instance. Why is tobacco bad for ulcer patients? Is it because it stimulates hypersecretion or increases acidity, or because of the vasoconstrictor effect on the blood vessels at the site of the lesion? In Buerger's disease one can observe within twenty-four hours a change in the appearance of an ulcer of the foot following a restriction of smoking. Pilocarpine exhibits a similar effect experimentally.

Massive Hemorrhage from Peptic Ulcer^{*}

A Study Based on Vital Statistics of the City of Seattle During Four Years and on Personal Experience in Private Practice

By

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and

WILLIAM S. COLE, M.D.

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PERUSAL of recent literature (2, 4, 6, 7, 8, 10, 11, 14, 15, 17, 23) shows remarkable variations in mortality from massive hemorrhage from peptic ulcer as reported from large charity hospitals. Most authors reporting from such institutions give mortality rates varying from 10 to 30 per cent. On the other hand, Finsterer (14) of Vienna, reports a mortality of 5 per cent in emergency surgery on bleeding ulcer. Lahey expects a 5 per cent mortality from bleeding ulcer. Hurst (13) reports 4.8 per cent mortality from Guy's Hospital, and states, "The danger of hemorrhage from peptic ulcer has been greatly exaggerated in a number of recent papers." He feels that in private practice the mortality is between 1 and 3 per cent.

Two years ago we (18) presented a study of our private patients suffering from gastric hemorrhage from peptic ulcer, together with remarks on vital statistics and peptic ulcer. We showed that the great majority of deaths from hemorrhage occurred in older patients—a point not previously emphasized. Allen (17) simultaneously and independently confirmed our conclusions that the age of the patient with bleeding ulcer is the most important factor in prognosis, and that in the age group above 50 years the mortality rate is approximately 30 per cent. Since that time a number of writers have remarked on the higher mortality in older people. Rankin (24) is the most recent advocate of emergency surgery for massive hemorrhage from peptic ulcer in persons past 50 years of age. Pfeiffer (22) is another of those recently advocating surgical treatment in older people; and other writers are now advising surgery for older patients suffering from massive hemorrhage.

Surgical treatment of hemorrhage has been championed by Finsterer (14), who feels that immediate operation for bleeding ulcer is always indicated and that no patient should be refused immediate operation. At the other extreme, Hurst (13) feels that operation for hemorrhage is rarely if ever indicated. A review of articles for several years just past reveals, however, that emergency surgery has rarely been undertaken. Repeatedly the idea is expressed that those patients whose illness will result fatally cannot be separated by clinical evidence from those who will survive; that emergency surgical mortality is much higher than that of medical supportive treatment; and that hence we should not increase mortality by emergency attempts at surgical control of hemorrhage from peptic ulcer.

STATISTICAL FALLACIES

Two years ago we were profoundly impressed with the difficulty of correlating statistical studies. Some authors have figures on all admissions for hemorrhage, others include only those severe cases which we call massive hemorrhage. Some record only cases with hematemesis. Some authors include and others exclude cases operated upon in an attempt to save life after the failure of medical measures.

Crohn (23) has just published a scholarly presentation on gross hemorrhage from peptic ulcer in which he calls timely attention to the statistical shortcomings of ten authors, including the writer. We had become entangled two years ago in the same remarkable maze of discrepancies which he has found, and we had tried to steer clear of such difficulties.

Crohn's paper (23) has been read carefully, and he seems to have gotten into as much trouble statistically as anybody else. Study of his tables shows that he has included 40 anastomotic bleeding ulcers with no deaths. Anastomotic ulcers are hardly, in our judgment, to be classed with unoperated ulcers. Excluding these his mortality for gross bleeding from peptic ulcer is raised from 6.5 per cent to 8 per cent; and if, as he states, two-thirds were severe hemorrhages, then his mortality from massive hemorrhage is 12 per cent. He excludes 75 cases operated upon for hemorrhage, though he writes, "35 patients over the age of 45 were operated, and 15 succumbed (46 per cent)* . . . Most of them represented the futility of medical means and conservative patience." There were 5 other deaths following operation in his series, presumably younger patients. We have found it impossible to confirm the arithmetic of percentages as shown on his charts, for the arithmetic appears grossly in error. If the 40 anastomotic ulcers are excluded, there were 34 deaths in 251 cases of chronic peptic ulcer with active hemorrhage, or a mortality rate of 13.5 per cent for gross hemorrhage from peptic ulcer, and for massive hemorrhage it should be one-third higher, or 20 per cent. This last figure is identical with that worked out at the King County Hospital in Seattle.

CLINICAL STATISTICS

Our clinic, since 1919, has observed 1076 patients suffering from peptic ulcer. The incidence of peptic ulcer and its acute complications per 10,000 patients admitted to the clinic is approximately:

Peptic ulcer	150
Acute perforation of peptic ulcer	9
Active gross hemorrhage	16
Active massive hemorrhage	7
Fatalities from hemorrhage	1

^{*}From The Mason Clinic.
Read before the American Gastro-Enterological Association, Atlantic City, May 1-2, 1939.

One fatality due to hemorrhage from peptic ulcer per 10,000 patients admitted to a private clinic, where gastro-intestinal cases are common, prompts the observation that many physicians in general practice may go through a busy lifetime without seeing a fatality from massive hemorrhage from ulcer.

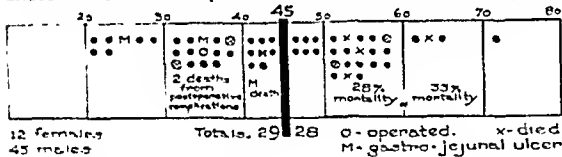
Tabulation of our histories shows that hemorrhage is recorded in 208 patients, or 19 per cent of all patients with peptic ulcer. Active hemorrhage has caused 113 patients to consult the clinic. Half of these patients were having only moderate loss of blood, evidenced by melena or hematemesis in moderate amount, without serious symptoms. We have classified such cases as *gross hemorrhage* and have not included them here.

The other half were suffering from serious blood loss, with alarming symptoms of exsanguination. These cases have been classified as *massive hemorrhage*. The classification of hemorrhages as moderate or massive must be a matter of clinical judgment. We diagnose *massive hemorrhage* when we find evidence of large loss of blood, with pallor, weakness, sweating, and prostration. Blood examinations in the first 48 hours of severe hemorrhage are of little value in estimating the amount of blood loss.

Careful study of case histories reveals, then, that only half of our patients with active gross hemorrhage were severely ill; therefore, our mortality percentages for massive hemorrhage should be halved if they are to be compared with those of authors who have listed mortality percentages based on *all* their cases of active gross hemorrhage.

THE MASON CLINIC 57 Active Massive Hemorrhages Peptic Ulcer

EXCLUDING 56 CASES GROSS BUT NOT MASSIVE HEMORRHAGE



SEVERITY OF PAST ULCER HISTORY	
Grade I	12
Grade II	18
Grade III	19
Grade IV	8
Total	57

ULCER SYMPTOMS AT TIME OF HEMORRHAGE	
39	quiescent
18	active

*5 OF 6 DEATHS FOLLOWED FIRST HEMORRHAGE.

Chart 1

MASSIVE HEMORRHAGE

As already stated, and as shown on Chart 1, 57 of our 113 cases of active gross hemorrhage were classed as massive hemorrhage. These patients all bled profusely and developed the classical signs of severe hemorrhage, and 6 older patients bled to death, including 2 exsanguinated patients who were operated upon after prolonged attempts at control of hemorrhage by medical means.

Further analysis shows that of those operated upon for control of hemorrhage, 3 deaths occurred in patients under 45 years of age; 1 was bleeding from a gastrojejunal ulcer, and 2 patients died from complications following operation but not from hemorrhage.

The death of 3 younger and 6 older patients gives a gross mortality of 15 per cent for massive hemorrhage from ulcer. The 6 deaths of patients above 45 years were due to exsanguination from chronic bleeding peptic ulcer, a mortality from hemorrhage of 11 per cent. If this 11 per cent be halved, since half of our cases of gross hemorrhage were not considered as massive hemorrhage, the figure of 5 per cent used by several writers as the mortality from hemorrhage in private practice is approximated. Of the 6 fatalities in older patients, 5 occurred during their first hemorrhage.

The histories of these patients with critical hemorrhage have been carefully tabulated in an attempt to evaluate the severity of the past symptoms. More than half gave histories of relatively mild symptoms. Neither chronicity, severity, age, nor sex has given a clue as to which ulcers are likely to bleed. A study of the histories also shows that at the time of massive hemorrhage only one-third of the patients were having severe symptoms due to ulcer. Two-thirds of the massive hemorrhages occurred during relatively quiescent periods.

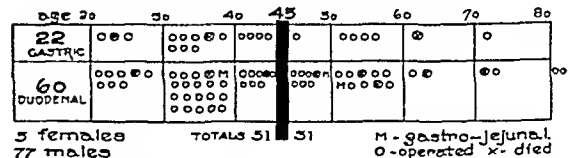
On charting ages by decades, it is apparent that half of all 208 patients with gross active hemorrhage—mild and severe—admitted to our clinic were below 45 years of age. If the time of the first gross hemorrhage is charted from 208 histories, 60 per cent were under 45 years of age when the first hemorrhage occurred.

MASSIVE HEMORRHAGE AND ACUTE PERFORATION

The Virginia Mason Hospital has, since 1920, admitted 82 patients suffering from acute perforation of peptic ulcer, and all were operated upon. Massive hemorrhage accompanied acute perforation in four instances only, and all four survived operation. Chart 2 gives the ages by decades of 82 patients admitted to the hospital for acute perforation, and shows that 51 of the patients were under 45 years of age. By decades, we find that 28 patients were in the thirties, 21 were in the forties, and 14 in the fifties. Two patients past 80 years of age recovered following operation for perforation.

THE MASON CLINIC 82 Acute Perforations Peptic Ulcer

(11 DEATHS*)



55 PERFORATIONS DURING QUIESCENT SYMPTOMS
27 PERFORATIONS DURING ACTIVE ULCER SYMPTOMS
4 PATIENTS HAD A PREVIOUS DIAGNOSIS OF ULCER
2 OPERATED AFTER 24 HRS.

MORTALITY	
under 45 yrs.	9.8%
over 45 yrs.	19.3%
gross	13.4%

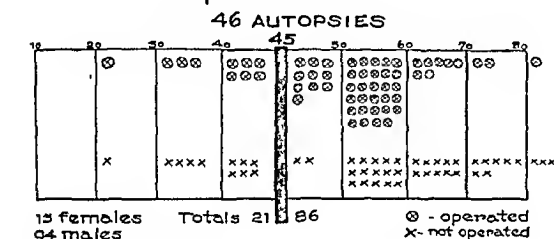
Chart 2

Eleven deaths followed operation, a gross hospital mortality of 13.4 per cent. The visiting staff of the

hospital operated upon 21 patients, all within 24 hours, with 4 deaths, mortality 20 per cent; The Mason Clinic operated upon 61 patients, with 7 deaths, mortality rate 11.5 per cent. The Clinic mortality for 56 acute perforations of peptic ulcer operated upon within 24 hours is just under 9 per cent. The Clinic cases include 3 patients with gastrojejunal perforation who recovered and 2 operated upon more than 24 hours after perforation who died.

Only 4 patients admitted for acute perforation knew that they had peptic ulcer before the perforation occurred, indicating the rarity of a severe ulcer history in cases that perforate. Two-thirds of the acute perforations occurred in periods in which ulcer symptoms were quiescent.

1935 - 1938 SEATTLE VITAL STATISTICS 107 Deaths Acute Perforations Peptic Ulcer



NO ACUTE PERFORATED GASTRO-JEJUNAL ULCER NOTED
Chart 3

Chart 3 shows 107 fatalities from acute perforation, with 46 autopsies—records taken from the Vital Statistics of Seattle. Surgery must have saved many lives, for only one-fifth of the deaths occurred in persons under the age of 45, though most perforations, as shown above, occur in younger people. The vital statistics show that 49 patients died without having been operated upon. No case of gastrojejunal perforation is noted in the vital statistics. Statistics have often shown that females rarely suffer from acute perforation. Recently an incidence of 2 per cent of females is reported from Detroit (20) in a large series of acute perforations. Yet when all deaths in a large city, Seattle, are considered, we find that 12 per cent were females.

VITAL STATISTICS AND MASSIVE HEMORRHAGE

There is a satisfaction in the certainty that all deaths in Seattle must be recorded in the Bureau of Vital Statistics and therefore have been available for this study. Chart 4 shows that 216 deaths certificates give peptic ulcer as the primary or contributing cause of death during the four years of 1935 to 1938 inclusive, and that 93 autopsies (43 per cent) are recorded. The high percentage of autopsies is due to the excellent autopsy service at the King County Hospital, and to the fact that most ulcer deaths have occurred either there or in private hospitals.

These 216 death certificates have been reviewed. Seventy-two certificates recorded hemorrhage as a

*Actually 43 per cent.

1935 - 1938 SEATTLE VITAL STATISTICS 216 Deaths from Peptic Ulcer 93 AUTOPSIES

MASSIVE HEMORRHAGES	55
ACUTE PERFORATIONS	107
POSTOPERATIVE DEATHS	24
OTHER CAUSES	30

Chart 4

factor in the fatal outcome. It seems improbable that any physician would omit hemorrhage from the death certificate if he felt that the patient died from hemorrhage. We investigated each of the 72 cases through hospital records or through the physician who signed the certificate. The deaths from active massive hemorrhage were actually 55 in number, with 24 autopsies.

Four deaths from hemorrhage were caused by bleeding from gastrojejunal ulcers, and in two cases fatal hemorrhage occurred years after the repair of acute perforations. Seven deaths followed late operation after medical failure to control hemorrhage. Ten fatalities were in females, 45 in males. The King County Hospital had as many fatalities as the total of the private hospitals, although the County Hospital averages but half as many patients as the total of the private hospitals.

Chart 5 shows the distribution of all fatalities in age decades. The youngest patient was 39 years old,

1935 - 1938 SEATTLE VITAL STATISTICS 55 Deaths Massive Hemorrhage Peptic Ulcer 24 AUTOPSIES

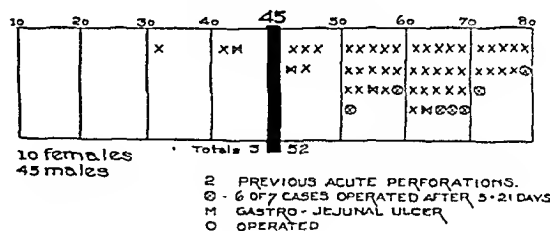


Chart 5

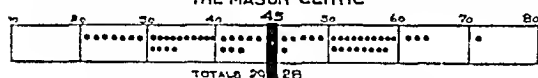
the next youngest 44; all others were more than 45 years old. The age incidence by decades shows 7 deaths in the forties, 16 in the fifties, 20 in the sixties, 11 in the seventies.

The rarity of fatal hemorrhage from peptic ulcer before 45 years seems proved by the fact that only 2 of 51 fatalities from chronic peptic ulcer hemorrhage occurred in patients under 45 years old, or 4 per cent of all deaths from this cause. Fatal hemorrhage from

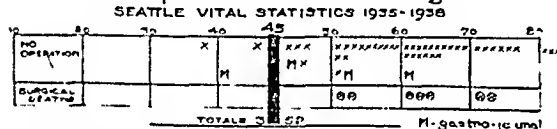
peptic ulcer in younger people is so rare that we are probably never justified in operating on such a case as an emergency.

The percentage of fatalities from exsanguination above 45 years presents a different picture. Of 51 cases of fatal hemorrhage from peptic ulcer, 49 were in patients above 45 years. We must recognize that fatal bleeding occurs in approximately 30 per cent of serious hemorrhages in older people. The surgeon is certainly justified in attempting to stop such hemorrhages by operative measures. The internist needs surgical consultation promptly in serious hemorrhage when the patient is in the older group; and operation, when indicated, should be done promptly, not after many days' delay.

57 Massive Hemorrhages Peptic Ulcer THE MASON CLINIC



55 Peptic Ulcer Hemorrhages SEATTLE VITAL STATISTICS 1935-1938



208 Clinical Histories - THE MASON CLINIC AGE AT TIME OF FIRST GROSS HEMORRHAGE.

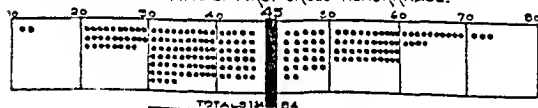


Chart 6

Chart 6 shows the remarkable contrast between the incidence by age decades of massive hemorrhage as compared with first hemorrhages from peptic ulcer. It also contrasts the fact that massive hemorrhages occur with equal frequency below and above the age of 45; yet vital statistics show that nearly all fatalities occur in the older group.

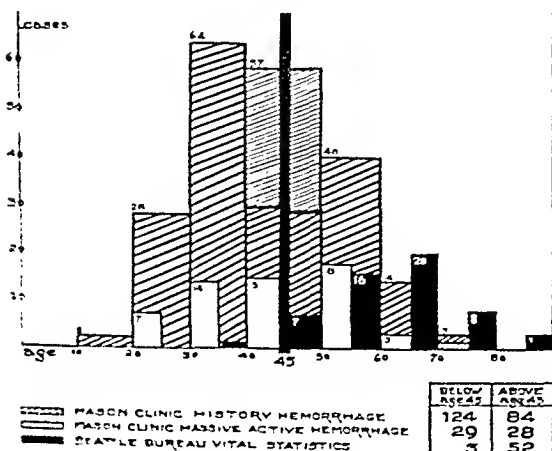


Chart 7

Chart 7 shows that the clinician sees most gross hemorrhages in the thirties, and most massive hemorrhages in the fifties. Deaths are most common in the sixties. The blocking of the chart indicates the curves of incidence of massive hemorrhage, and of all first hemorrhages, as shown by clinical histories; and of all deaths from massive hemorrhage, as shown by vital statistics.

SURGICAL TREATMENT

Our small experience in surgical treatment has not included enough cases or successes to warrant undue surgical enthusiasm. Emergency operation as a late measure has failed to save two of our patients. Two younger patients operated upon as emergencies have died from postoperative complications, but not from hemorrhage. Two other younger patients were operated upon because of exsanguination, and they survived operation; though we now suspect that they might have survived without operation.

We believe that immediate operation must be considered for older patients in every serious hemorrhage from peptic ulcer; for only thus can we hope materially to reduce a mortality rate of approximately 30 per cent in these patients. Early operation is emphasized by Finsterer (14) and Allen (17), and our small experience confirms their remarks. Delay for days to allow repeated supportive measures before operation results in almost one hundred per cent fatalities. Apparently operation must be undertaken before the blood-making ability and other reserves of the patient are exhausted. And our statistics indicate that only older patients should be operated upon.

We feel furthermore that any surgical statistics of successes in life-saving by emergency operation for hemorrhage when ages are not tabulated should be read with skepticism. Vital statistics prove that practically no deaths due to hemorrhage from peptic ulcer occur under the age of 45 years, if the surgeon can be restrained. Surgical intervention should be undertaken only on older patients, and reports of surgical successes should include the ages of the patients operated upon expressed in decades. If the surgeon can reduce the mortality materially below 30 per cent in the older group, then surgery is certainly the procedure of choice in older patients.

CONCLUSIONS

1. Vital statistics show that 4 per cent of all deaths from massive hemorrhage from peptic ulcer occur under the age of 45.
2. Vital statistics show that 96 per cent of all deaths from hemorrhage from peptic ulcer are in patients above the age of 45.
3. Vital statistics indicate that emergency surgery for bleeding ulcer is not justified on patients less than 45 years of age.
4. Early emergency surgery for massive hemorrhage from ulcer in patients above 45 years of age should save many lives.
5. No younger patients in our series of hemorrhages from peptic ulcer have died except as an immediate or late result of surgical interference.
6. The commonly quoted mortality rate of 5 per cent for peptic ulcer hemorrhage is approximately one-sixth of the actual mortality rate in older patients having massive hemorrhage from peptic ulcer.

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Results of Treatment of Massive Gastric Hemorrhage

By

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THE treatment of massive gastric hemorrhage, as evidenced by hematemesis, melena or both, has been the subject of much discussion in recent years. Twelve years ago, when I read a paper on this subject at an American Medical Association meeting, I was still under the impression that such a hemorrhage was practically never a cause of death and I could find no record of any fatality at the Long Island College Hospital during the six or seven years we had been using the treatment recommended. It was suggested merely as a method of making the patient more comfortable, shortening his stay in the hospital and making it possible to determine the cause of his hemorrhage sooner than by the older methods of treatment. Previously the treatment of hemorrhage had been pretty well standardized, consisting of at least six weeks' rest in bed, an initial period of starvation, the parenteral administration of saline, glucose or whole blood, the use of coagulants locally and parenterally, ice externally and internally, lavage with astringents or escharotics, and at times operation with no attempt at laboratory or Roentgen diagnosis for from 6 to 10 weeks. Even today such treatment, in whole or in part, is in pretty general use, although statistics have shown the relatively high mortality attendant upon it.

Essentially the treatment recommended by me consists of immediate feedings of a soothing, coagulant, nutritious food formula, the avoidance of sudden increase in blood volume or pressure, the application of warmth to the body, and resort to operation only if the hemorrhage is shown to be intractable.

It is an interesting fact that in taking histories of patients with peptic ulcer, we so often discover that they have had massive hemorrhages for which no physician was consulted, and immediately following which the patients ate as before, went back to work the next day and experienced no particular after-effects except malaise for a week or so. In recent years, Meulen-gracht also has called attention to this fact, and his method of treatment, based on this knowledge, has received considerable commendation because of the much reduced mortality following its use. It is quite evident

therefore, that our previous prolonged starvation periods and intensive treatments were not only superfluous, but that they unnecessarily prolonged the patient's recovery. It is therefore worth while that a brief summary of some of the factors present in a case of hemorrhage should be considered.

PATHOLOGY

Whereas nearly all patients with gross hemorrhage are suffering from a complication of peptic ulcer, it is always well to remember that hemorrhage may be the first manifestation of a carcinoma or of an esophageal varix, that recurrent hemorrhage may result from bleeding polyps or even from a severe gastritis, and that occasionally blood dyscrasias or purpuras may show bleeding from the gastric mucous membrane. Massive hemorrhage in an ulcer case usually results from injury to the wall of a small blood vessel, and it has been pointed out that if the vessel has been cut across transversely, retraction of the bleeding stump is facilitated and hemorrhage is only transient, whereas if the injury has resulted only in the sloughing out of a side of the vessel, retraction is very difficult and prolonged bleeding is the rule. In old, indurated ulcers, usually caused by perforation or partial perforation with resultant excessive reaction in and around the ulcer area, exhibiting a horny infiltration with perigastric or periduodenal adhesions, a bleeding vessel may be held stiffly open, unable to retract. This generally results in continuous and profuse hemorrhage until the patient is exsanguinated. Even on the operating table such bleeding cannot be stopped without extensive resection, fatal to the patient. Fortunately this type of case is rare and in our experience hemorrhage has usually occurred in new and often rather small ulcers, which heal rapidly, so that in a series of one hundred and twenty cases studied by fractional gastric analysis and thorough Roentgen examination within sixteen or eighteen days of the onset of bleeding, we found no evidences of ulcer in fifteen cases (see Table I). In our series of cases the age varied from sixteen to eighty-two years, but the average was forty-two years, which is in agreement with statistics by other authors. The males (88) also

predominated over the females (32). There were only three colored patients in the series.

SYMPTOMS

Massive hemorrhage is, of course, manifested by the vomiting of a considerable amount (8 ounces or more) of fresh blood, by the passage of large tarry stools, or both. It would be expected that hematemesis would always be accompanied by melena, and in our

TABLE I
Gastric hemorrhage

120 Cases—Findings	
Duodenal Ulcer	78—60%
Gastric Ulcer	16—13%
Gastric and Duodenal	4—3%
Marginal or Jejunal	4—3%
No Ulcer Found	15—12%
Pyloric Stenosis	6—5%

series of one hundred and twenty cases (see Table II), 67% showed this combination. Twelve patients failed to show gross blood in the stools, having undoubtedly vomited most of the blood which had spilled. Only 23% of our cases showed melena alone—patients do not consider this as serious as hematemesis and do not come to the hospital unless in very bad condition. A history of previous ulcer symptoms was obtained in 86% of our patients. Hemorrhage occurred as a first symptom in but seventeen patients or 14%, all the others having experienced more or less pain preceding the onset of bleeding. A history of previous massive hemorrhage was obtained in 39% of our cases, of whom eleven or 9% had had two or more previous hemorrhages. Usually these previous hemorrhages had been recognized as such by the patients, but occasionally only a history of an attack of fainting and dizziness, accompanied or followed by vomiting, the nature of the vomitus not having been noted, or by "diarrhea," with no observation of the stools. Succeeding

TABLE II
Gastric hemorrhage

120 Cases—Symptomatology	
Hematemesis (alone)	12—10%
Melena	28—23%
Both	80—67%
Previous Ulcer	104—86%
Previous Hemorrhage	47—39%
Previous Operations	4—3%
Hemorrhage first symptom	17—14%

pallor, weakness, thirst and general malaise had often been attributed, even by their physician, to "ptomaine poisoning" or a "heart attack."

EXAMINATION

When first seen, the patient who has had a massive hemorrhage is in shock, appears frightened and apprehensive, is chilly and complains of great thirst. Marked pallor, a rapid, weak pulse, low blood pressure and cold extremities demand immediate attention. Although the need is for absolute rest, making it unwise to dis-

turb the patient by too complete and thorough general physical examination, it is nevertheless desirable to determine as accurately as possible, by questioning and observation, whether the bleeding has originated in the mouth, nose, throat or pulmonary tree, whether hepatic enlargement or gross abdominal tumors are present or whether there is evidence of a perforation accompanying the hemorrhage. While complete physical examination should be deferred until cessation of the hemorrhage, certain laboratory tests should be carried out immediately.

Blood counts, performed daily for three days, and then every two or three days, may show normal findings the first day, before blood volume has been replaced by absorption from the tissues. During the next twenty-four or forty-eight hours there is a steady fall in the count, even though all bleeding may have stopped, and after two or three days more a steady rise occurs. Table III shows the lowest points to which the red blood cells and hemoglobin fell, the average for our series of one hundred and twenty cases being 2,800,000 and 57% respectively, the lowest 1,100,000 and 14%. The white blood cells showed but slight variations from the normal. A distinctly increased

TABLE III
Gastric hemorrhage

120 Cases—Laboratory Findings			
	Lowest	Average	
Hemoglobin	14%	57%	
R. b. c.	1,100,000	2,800,000	
Average Gain	20%	1,700,000	
Urea N Highest 70 Average 32			
<i>Gastric analyses</i>			
	Highest	Lowest	Average
Free HCl	110	0	55
Total Acidity	140	10	75

leucocyte count should therefore be regarded with great suspicion that a perforation or other complication may be present. The same would be true of a marked rise in the percentage of polymorphonuclear leucocytes, which is usually normal or very slightly increased, with an occasional patient showing an actual leucopenia. Blood chemistry findings were interesting in that our cases showed a blood urea nitrogen averaging 32 mg. per 100 cc. with a high point at 70 mg. Usually the findings returned to normal within a few days or a week. Failure to do so was often an indication that bleeding was continuing, as pointed out by Ingegno four years ago, in a report emanating from our service at the Long Island College Hospital. Blood coagulation tests—coagulation and bleeding time, platelet count and prothrombin estimation—showed increase in all factors, except in the rare cases of blood dyscrasia. In view of this finding we long ago realized the uselessness of routine treatment by coagulants.

Fractional gastric analysis (Table III) was not done in our cases until nearly two weeks after the hemorrhage. At this time a fractional analysis after intramuscular injection of histamine disclosed that the usual secretory curve was one indicating a reflex, con-

tinued secretion, with the highest free HCl 110 and Total Acidity 140 and the average free HCl 55 and Total Acidity 75. In less than one-half of our cases was any visible blood found in the contents, indicating that rapid healing had taken place. Overnight retention was, of course, found in the stenosis cases.

Roentgen examinations were begun a day or two after the gastric analysis, unless this showed considerable bleeding still to be present. The average day for the beginning of the gastro-intestinal series was the sixteenth. During this period there had been an opportunity for the smaller ulcers to heal so that in our one hundred and twenty cases (see Table I) 12% showed no lesion. Of the others 13% showed definite gastric ulcer and 60% duodenal ulcer, and 3% showed both. Marginal or gastrojejunal ulcer was found in 3%. Pyloric stenosis was found in 5%. In all possible instances the patients were followed until Roentgen evidence of complete healing had been obtained or after operation had been performed.

PHYSIOLOGY

A consideration of the physiological principles to be considered following a massive gastric hemorrhage is of great help in developing a satisfactory course of treatment. When a large hemorrhage occurs from any cause, the immediate reaction is shock, as evidenced by dizziness and faintness, due to cerebral anemia and anoxemia, a definite lowering of blood pressure, and a compensatory increase in pulse rate. The patient may actually lose consciousness or may be merely so dizzy as to be compelled to lie down, the recumbent posture making it easier to maintain circulation. The lowered blood pressure and diminished blood volume result in a decrease in the force and volume of flow through the injured blood-vessel, facilitating the formation of a clot and thus stopping the hemorrhage. Meanwhile all coagulation factors are being mobilized, prothrombin is increased in amount, platelets multiply and at the site of bleeding there is an accumulation of factors concerned in healing and the combating of infection—lymphocytes, reticulocytes, round cells, etc. The very gradual replacement of blood volume by absorption of water from the tissues permits the formation of a firm clot and its organization. The stomach usually becomes filled or partly filled with blood, even though some may be vomited. The filled stomach shows ordinary slow peristalsis and the blood combines readily with hydrochloric acid and pepsin, thus preventing these from attacking the edges of the bleeding vessel or the thrombus forming within. So far, nothing has occurred to interfere with prompt and complete control of the bleeding. Soon the stomach empties itself, the much-stimulated and powerful gastric secretion is left free to attack vessel and thrombus, and hunger contractions, intermittent, and increasing in force, tend to cause sudden and drastic changes in the pressure behind the thrombus, making it liable to be blown out. Fortunately, however, the patient is thirsty and hungry, and if he takes food in moderation and not enough fluid internally to increase blood volume materially, hunger contractions are stopped and gastric secretions again become fixed with the food. The general weakness due to the hemorrhage induces the patient to stay in bed, thus tending to maintain the low blood pressure so desirable during the period of organization of the thrombus. Thus, if nothing is done to the patient, if he is allowed to follow his own

impulses and if there is nothing present at the site of bleeding to interfere with the retraction of the bleeding vessel and formation of a thrombus (see discussion of pathology, above), everything tends to promote such clotting, and the patient recovers more or less rapidly from the results of the hemorrhage.

On the other hand, if the patient is treated according to the older standard methods, let us see what happens. Starvation for a few days (as also aspiration of all stomach contents) results in intermittent periods of intense hunger contractions, alternately increasing and decreasing the irritation and pressure at the bleeding point, and tends to loosen the clot during this period before it has become firmly organized and adherent to its vessel wall. Also, the gastric juice, with no stomach contents to attack, may dissolve out the clot or actually attack the vessel wall, which is not protected from digestion as is the mucosa. Besides this, starvation increases the patient's restlessness and lowers his resistance. Sudden increase in blood volume and pressure, induced by transfusion or parenteral

TABLE IV
Gastric hemorrhage

Mortality—Older Methods			
Author	Cases	Deaths	Per Cent
Bulmer	467	48	10.7
Goldman	319	39	11.1
Christianson	259	23	7.9
Aitken	231	20	8.5
Chiesman	191	48	25
Jankelson	189	18	9
Burger & Hart	117	21	18
Crohn	94	1	4.2
Lynch	52	10	19
Huntton	41	6	13
McCliffer	40	3	7.5
Total	2,066	240	11.6

administration of other fluids, will tend to blow out the clot, and three of the deaths in our patients seemed to be attributable to this cause, transfusions or infusions having been given before the patients came under our care. The use of coagulants locally or parenterally, while doing no harm, is practically never required, all coagulation factors being naturally increased in potency. The use of ice externally is contrary to the generally accepted dictum that warmth is necessary in shock, and besides makes the patient miserable and cold, and ice internally can have no effect except to increase the circulation in the gastric wall, an undesirable result. Lavage, whether with water, astringents or other agents may conceivably tend to increase bleeding. Operation as a routine procedure is unnecessary, and in the cases showing the bleeding vessel held in a mass of horny scar tissue and surrounded by adhesions due to perforation or deep penetration, may present such mechanical difficulties that the operative mortality is excessive. The mortality from the older routine treatment, without operation, in 2,066 cases, gathered from literature here and abroad and shown in Table IV varied from 4.2%

TABLE V
Gastric hemorrhage

Mortality Operated Cases			
Author	Cases	Deaths	Per Cent
Pfeffer	22	5	22.7
Atkes	21	7	32.3
Burser & Hart	20	5	25.0
Janfelson	11	3	27.0
D'Abreu	10	3	30
Hinton	8	4	50
Total	92	27	29.3
Early operations (within 48 hours)			
Funsterer	16	2	4.3
Gordon Taylor	22	2	9
Total	68	4	5.8

to 25%, with an average of 11.6%. The general operative mortality (Table V) was 29.3%, but as in most instances these operations had been done later, after it had been found that bleeding was showing no tendency to stop spontaneously, we are comparing this mortality with that where operation had been performed within the first forty-eight hours when it was only 5.8%.

TREATMENT

The treatment recommended by me originally, based upon physiological considerations and resulting in a mortality of only 2.3% in a series of one hundred and seventy-three cases treated by D'Albora and myself (Table VI) has been changed in its minor details, but the principles involved have remained the same. Meulengraecht, whose treatment is along similar lines, has had a slightly lower mortality, but I believe that as the mortality really depends on causes which are irremediable, it will be found to remain in the neighborhood of 2% in long series of cases. Thus an analysis of the reason for our six deaths (Table VII) shows that while three died soon after large transfusions and therefore were not really treated by our method, the other three, all submitted to autopsy, showed the type of complication which would cause persistent

TABLE VI
Gastric hemorrhage

Mortality—Newer Treatments			
Author	Cases	Deaths	Per Cent
Meulengraecht Method:	Meulengraecht	28	3
	Vendt	28	7
	Total	57	10
Author's Method:	D'Albora	55	1
	Andrews	120	3
	Total	175	4

bleeding which could not be controlled except by too-extensive surgical procedures.

Based upon physiological indications previously discussed, the treatment we recommend is as follows:

Shock should be treated by absolute rest in bed. Occasionally in a restless patient, morphine hypodermatically is required during the first twenty-four hours, but psychological treatment usually suffices to allay apprehension and stimulate cooperation. Explaining that the condition is not serious, that rest will encourage clotting and prevent continuing hemorrhage and that the restricted diet is necessary to stop the bleeding, we find our patients soon lying quietly in bed, often reading the paper or listening to the radio. A few hot water bags help to maintain body heat and make the patient comfortable, but over heating should be avoided, as this is distressing and weakening. I know that many patients have been so badly frightened by the hustle and bustle attending the measures resorted to under the old methods of treatment that it would be weeks before morale was restored. With attendants calm and encouraging, with no screening-off of the bed, with, if possible, a convalescent hemorrhage case in the next bed to encourage him, the patient, except for his pallor, ap-

TABLE VII
Gastric hemorrhage

120 Cases—Mortality

6 Deaths:

1. Exsanguinated—transfusion—died 24 hours.
2. Large transfusion.
3. Transfusion plus glucose.
4. Autopsy: gastric—old perforation, horny induration.
5. Autopsy: duodenal—old perforation, horny induration.
6. Autopsy: pyloric stenosis—prepyloric ulcer.

3 Deaths after transfusion, not counted.

Corrected mortality—3 cases—2.5%.

pears no different from other uncomplicated ulcer patients in the ward.

The *bleeding area* is treated by local applications of food. I have pointed out the desirability of controlling the undesirable and actually harmful hunger contractions and of preventing digestion of clot and injured vessel wall, by keeping food in the stomach. If the food, in addition to being soothing, combining readily with hydrochloric acid and not overstimulating its production, also has the effect of encouraging blood coagulation, we have an ideal combination. Gelatin has long been known as an excellent coagulant, whether locally applied or parenterally administered, and it is readily combined in a soothing liquid food mixture. Formerly our gelatin solution was made with water, and contained sugar and fruit juice to give it nutritive value (see Table VIII). After two days of these feedings, high calorie gruel and milk mixtures were substituted for every other gelatin feeding. In recent years the gelatin has been combined with milk, cream and glucose, and flavored with coffee, tea, chocolate or vanilla, making a drink enjoyed by nearly all patients and found to be even more efficient than the aqueous mixture. The patients are given at least 1800 calories during the first day after the hemorrhage, feel better

TABLE VIII
Gastric hemorrhage

Feedings Immediately After Hemorrhage					
Gelatin-Milk Mixture:					
	Amt.	Carb.	Prot.	Fat	Cal.
Gelatin	30 gm.		27		100
Dextrose	60 gm.	60			240
Cream (20%)	100 cc.	3	3	18	180
Milk	900 cc.	36	27	27	550
Totals		99 gm.	57 gm.	45 gm.	1000 Approximately

Formula to be made fresh every 12 hours, kept cool, but not in refrigerator, to prevent jelling.
Given cool or warm. Plain or flavored.

First 4 days: 6 oz. every 2 hours.

5th and 6th days: add to 4 of above feedings one of any of following foods:

- 1 egg—soft boiled, poached or raw
- cereal—3 oz.
- custard, jello or ice cream.

7th and 8th days: add 2 of above foods to each of 3 feedings.

9th day: Ulcer diet.

NOTE: At times the patient cannot tolerate the thick milk-gelatin mixture. In such cases use the gelatin-water formula, as follows:

Gelatin-Water Mixture:

	Amt.	Carb.	Prot.	Fat	Cal.
Gelatin	30 gm.		27		100
Dextrose	90 gm.	90			360
Juice of 2 oranges		20			80
Water	1,000 cc.				
Totals		110 gm.	27 gm.		540

and are in a better condition to promote healing of the lesion. In patients allergic to milk or who do not take the formula easily the old gelatin-water solution is still used. The routine as to quantities prescribed is shown in Table VIII, and Table IX shows the routine ulcer diet which I have used for years and which, in hemorrhage cases is gradually added to after a month or six weeks. Although repeated tests on our patients' blood and urines have shown no diminution in the cevitic acid content, we have in recent years added vitamin concentrates to our diets.

Anemia does not as a rule require special treatment, the rapid, spontaneous rise in blood counts having already been mentioned. However, repeated blood counts are done, blood chemistry determinations are made, blood coagulation tests are performed and blood pressure records are kept, so that any evidence of continued bleeding may be promptly observed and treatment instituted. The patient's blood is typed on admission and prospective donors are cross-matched, so that, if the patient shows a severe anoxemia, as evidenced by air hunger or a weak, thready pulse, small transfusions can be promptly given. Usually 150 to 200 cc. of blood is sufficient—more is undesirable. Although in our series of cases, small transfusions were given in the first ten days to seventeen patients, constituting 14% of the total number, in recent years the percentage has been less than 5%, as we have realized that even what appears like very serious bleeding will usually cease spontaneously if no extra fluid is suddenly added to the circulation. Iron, by

mouth or intramuscularly, may be given, but our statistics show that it has no particular advantage. Coagulants are very rarely required.

Constipation is encouraged—that is, nothing is done to disturb intestinal motility during the early days succeeding the hemorrhage. Mineral oil, one-half ounce per day, may be given after the second day, and, if required, oil retention enemas are administered after four or five days and thereafter as indicated. No other measures are ever used to produce defecation. All stools are examined for occult blood.

Operation for hemorrhage is a serious matter. While statistics, quoted above, have shown that operation performed as a routine in the first forty-eight hours after the onset of hemorrhage showed a mortality rate of less than 6% in the hands of two expert surgeons, yet, when we realize that only two or three per cent die when not operated upon, the risk of early operation would appear unjustifiable. When continued bleeding is present and exsanguination is imminent, resort to operation is attended by a very high mortality and surgeons are loth to operate. Surgery was refused in the cases in our series which died, because it was realized that the patient could not survive the double shock of hemorrhage and operation. Where operation is performed, extensive procedures, such as resection, are usually necessary, as pointed out previously in this article. The hemorrhage reported to have been stopped by simple gastro-enterostomy would undoubtedly have ceased spontaneously except where pyloric stenosis was definitely the factor which kept the bleeding vessel from retracting. Later operations for such complications as stenosis or walled-off perfo-

TABLE IX
Gastric hemorrhage

Ulcer Diet	
Breakfast:	
Milk 8 oz., with cream if desired.	
Cereal 5 oz., with milk or cream.	
Egg—1 soft boiled or poached.	
Bread or toast with butter, 1 or 2 slices.	
Fruit juice or stewed fruit (at end of meal).	
Mid-morning:	
Milk—8 oz., cream $\frac{1}{2}$ oz., dextrose $\frac{1}{2}$ oz., with cocoa if desired.	
Always with crackers, toast, bread or cake.	
Luncheon:	
Milk 8 oz.	
Baked or mashed potato or plain spaghetti.	
Egg—1 soft boiled or poached, or cream cheese.	
Bread and butter, 1 or 2 slices.	
Pudding, custard, gelatin, ice cream, or stewed fruits.	
Mid-afternoon:	
Same as mid-morning.	
Supper:	
Same as breakfast or luncheon.	
At bedtime and during night every 2½ hours, if awake—same as at mid-morning.	
Olive oil—½ oz. three times a day before meals.	
Mineral oil—½ oz. at bedtime.	
Water: ad lib.	
Salt: Not restricted.	
Vitamins: As required.	

ration with resulting deformities should be performed as indicated.

After-care. Two weeks after admission, when repeated stool examinations show absence of blood or only small amounts of occult blood, a fractional gastric analysis is done, and if no visible blood is present, Roentgen examination is begun the next day, thus giving early information as to the source of the

TABLE X
Gastric hemorrhage

120 Cases—Treatment	
Transfusion 1 to 10 days	17—14%
After 10 days	25—20%
Operations for Hemorrhage	None
For Pyloric Stenosis	5 (later)

hemorrhage and pointing out the indications for further treatment. Then focal infections are searched for and eradicated, such operations being preceded by transfusions if indicated. About 20% of our patients were thus given blood after the first ten days in the hospital (Table X). The patients can usually be allowed to go home within four or five weeks, to be followed afterwards in clinic or office.

SUMMARY

In summarizing, I shall present the following outline of the indications for treatment and the routine procedure in hemorrhage cases, taken from the Ward Manual of the Medical Service at the Long Island College Hospital.

INDICATIONS FOR TREATMENT

Condition	Treatment
Shock	Rest, warmth, morphine
Apprehension	Quiet, psychic treatment
Local Bleeding	Soothing, coagulant, ant-acid diet
Hunger Contractions	Frequent, nutritious feedings
Severe Anoxemia	Very small transfusions
Anemin	None or later iron and transfusions
Impaired Coagulability	Coagulants, blood, vitamins
Constipation	Mineral oil and oil enemas (4th day).

ROUTINE IN GASTRIC HEMORRHAGE CASES

1. Treat Shock by rest, warmth and morphine (latter only if required).

2. Quiet Apprehension, do not awaken. Keep bed in quiet location.

3. Treat Bleeding Area: Order Gastric Hemorrhage Diet and nothing else by mouth.

4. Type and match blood for transfusion. No transfusion in first ten days except for air hunger or very weak pulse. Then only 180 to 200 cc.

5. Special charting for blood pressure and feedings.

6. Blood count every 2 days. Marked anemia may require transfusion after ten days and iron after meals.

7. Blood Coagulation tests. Coagulation and bleeding time, platelet count, prothrombin—repetition and treatment as indicated.

8. Blood Chemistry (Urea Nitrogen particularly) on admission and at two day intervals until normal.

9. Test all stools for occult blood until this disappears.

10. If no defecation: Mineral oil, ½ ounce each night, beginning second night. Retention oil enema on fourth day and each night thereafter, if required.

TO BE AVOIDED

1. Ice: Externally, increases shock. Internally, stimulates gastric circulation.

2. Parenteral fluids: Increase blood volume and pressure—cause more bleeding. N. B. Small transfusions may be required in severe anoxemia. See Routine.

3. Stimulants (digitalis, adrenalin, etc.): Tend to increase bleeding. Only used in dire emergency.

4. Alkalies: Stimulate secretion. Irritate bleeding area.

5. Excitement or Worry: Increase shock and reaction may increase bleeding.

6. Examinations, manipulations or treatments, except as absolutely necessary, especially in first few days.

In closing I wish to thank my associate, Dr. S. C. Franco, for his valuable aid in gathering the statistics presented, to Dr. J. C. LaDue, a former interne, who permitted me to incorporate statistics he obtained from our hospital records, and which he will shortly present at the American Medical Association meeting in St. Louis, and to Dr. S. B. Thomas of Brooklyn, for permission to use operative statistics from a paper he read but did not publish.

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Gastro-Intestinal Hemorrhage From Otherwise Symptomless Lesions, With Special Reference to Duodenal Ulcer*

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HEMATEMESIS or melena, or both, are reliable evidence of gross hemorrhage from the upper portion of the gastro-intestinal tract, which may be due to a variety of causes. When such hemorrhage is associated with a history of upper abdominal pain or discomfort related to the digestive cycle and with other digestive disturbances, one logically assumes the presence of some type of intrinsic lesion of the stomach or duodenum until proved otherwise. Every now and then one sees patients whose sole complaint is the vomiting of blood and the passing of tarry stools, singly or repeatedly, and of varying degrees of severity. Such patients have never experienced pain, discomfort or indigestion. What are the circumstances that give rise to such a state of affairs, and to what extent do gastro-duodenal lesions, so-called silent, concealed or asymptomatic lesions, play a role?

DUODENAL ULCER AND DUODENITIS

For a number of years we have been cognizant of the fact that hemorrhage may be the sole manifestation of chronic duodenal ulcer, or of chronic duodenitis. As the former is the commonest gross lesion of the upper portion of the digestive tract encountered in American medical practice, such a manifestation is of great clinical import and interest.

The incidence of hemorrhage associated with otherwise asymptomatic duodenal ulcer or duodenitis was determined on the basis of a study of 1089 verified cases. In seventeen cases, or 1.5 per cent, hemorrhage was the sole sign of the lesion. In another twenty-four cases, or 2.2 per cent, in addition to hemorrhage, a history of vague or mild digestive disturbances elicited only on repeated questioning, was recorded. Thus, in a total of 3.7 per cent of the cases, painless hemorrhage constituted the outstanding, almost exclusive, manifestation of the ulcer. Considering the fact that only 20 per cent of duodenal ulcers give rise to gross hemorrhage, these figures are of interest because they indicate that hemorrhage is a painless, almost exclusive feature in 18.5 per cent of the cases of bleeding ulcers. There was another group of fifteen cases in which hemorrhage was the initial sign, and in which, after an otherwise symptomless period of variable duration of months to years, the characteristic pain and digestive disturbances eventually made their appearance.

It is obvious that hematemesis or melena, or both, can be the sole expression of a duodenal ulcer or its equivalent. It follows that if hematemesis or melena

can be the sole expression of an ulcer of the duodenum, it also can be that of any ulceration of the digestive tract, acute, subacute or chronic, situated anywhere between the lower half of the esophagus and the lower portion of the ileum. Even such a rare lesion as a diverticulum of the stomach may manifest itself in this way in view of the reports of Sutherland (1), and Brown and Priestley (2). The frequency with which painless hemorrhage occurs in cases of chronic gastric ulcer on the basis of our own material as yet has not been determined. Cases 1 and 2 are illustrative of chronic duodenal ulcer and chronic duodenitis, respectively.

Case 1. A woman, forty-nine years of age, registered at The Mayo Clinic February 1, 1938. In 1932, without provocation, she had experienced a sudden attack of nausea, profuse hematemesis, shock and syncope and thereafter passed tarry stools for a period of ten days. She had experienced a similar attack in 1936. Again, on January 15, 1938, she had noticed tarry stools and weakness for five days. At no time did she experience any epigastric pain or indigestion. The results of physical examination were essentially negative. The patient was of nervous temperament and hypersensitive. Gastric intubation was not done because of the recent hemorrhage. Roentgenologic examination of the stomach and duodenum disclosed deformity of the duodenal cap characteristic of chronic duodenal ulcer. In the absence of pain and other complications, medical treatment was recommended. The patient had enjoyed good health up to the time of our last report from her in March, 1939.

Case 2. A man, twenty years of age, registered at The Mayo Clinic, March 9, 1937. At irregular intervals since February, 1931, he had experienced attacks of melena, twice associated with moderate hematemesis, which in turn caused anemia and prostration. His most severe attack occurred in October, 1936. Intense social activities, such as fraternity "rushing" parties, provoked bleeding. He had never experienced pain or indigestion. Analysis of the gastric contents revealed 64 clinical units of free hydrochloric acid. Roentgenologic examination of the stomach and duodenum disclosed bulbar irregularity and irritability characteristic of duodenitis. Medical treatment was carried out. The patient was enjoying good health in March, 1939, when he was heard from last.

Of importance equal to, if not greater than, gastric or duodenal ulcer and gastric carcinoma as the cause of painless hemorrhage is chronic gastritis, benign tumor of the stomach, splenic anemia, biliary cirrhosis and certain late postoperative sequelae. Of less importance because of their comparative infrequency, yet of great clinical interest, are para-esophageal hernia, ulcer and neoplasms of the small bowel and of Meckel's diverticulum. There remains an indeterminate group in which it is impossible to ascertain defi-

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nately the cause of gastro-enteric hemorrhages, especially in the earlier stages of the process, owing to the complete absence of any objective data. As a matter of fact, in a considerable percentage of such cases, the cause of the hemorrhage may remain undetermined even after exploratory operation. In this group are not intended to be included those instances of silent solitary hemorrhage in which there has not been antecedent or subsequent developments.

CHRONIC GASTRITIS

The latent subclinical or asymptomatic nature of gastritis in its various forms has been substantiated by numerous observers on the basis of pathologic and gastroscopic observations. This fact, in addition to the high incidence of the disease as reported by competent gastroscopists, both in America and abroad, justifies the conclusion that chronic superficial and hypertrophic gastritis, if not the most frequent, is one of the most frequent causes of painless hematemesis and melena. Former statistical data relative to the various causes of gastro-enteric hemorrhage are of doubtful scientific value because, almost without exception gastritis as a factor has not been taken into consideration. The present tendency in many clinics and hospitals to carry out routine gastroscopic examination in all unexplained cases of gross hemorrhage has been a revelation in many ways but especially in the elucidation of the important role that superficial inflammatory mucosal lesions play in gross bleeding from the upper portion of the digestive tract. Recent gastroscopic examinations have demonstrated the fact that chronic duodenal ulcer is frequently accompanied by such superficial inflammatory lesions, as well as by simple erosion and submucosal hemorrhages and that the source of the bleeding usually attributed to the ulcer, on the contrary, is often found to be due to the superficial inflammatory lesions, simple erosion or submucosal hemorrhages.

Case 3. A man, thirty-two years of age, registered at The Mayo Clinic January 9, 1939. In 1932 and in 1937 he had experienced unexplained seizures of sudden weakness. In retrospect, this may have been due to melena, as the condition and color of the stools were not observed at that time. In February, 1938, the patient had experienced a similar attack, with vomiting of coffee-ground material. At that time, he had observed tarry stools. Again, in December, 1938, he had had an attack of melena and prostration, and three days later, hematemesis and melena, resulting in shock. The concentration of hemoglobin was 44 per cent. He had not experienced epigastric pain or indigestion at any time. Repeated roentgenologic examinations of the stomach and duodenum gave negative results. Gastroscopic examination disclosed a definite hypertrophic gastritis of the fundus. The tonsils were definitely infected and were removed in the hope that this infection was the source of the patient's difficulty.

BENIGN TUMOR

A paucity of symptoms and a great tendency toward bleeding is characteristic of the majority of benign tumors of the stomach. On that account this possibility should be excluded in every case of painless hemorrhage, or of obscure anemia that results from long continued occult bleeding. These lesions are not as infrequent as previously was supposed. Already 176 surgically verified cases of benign gastric tumor have come under our observation, exclusive of those found

at necropsy when death was due to other causes. Improved roentgenologic technic has made possible roentgenoscopic detection of the majority of these tumors, even the smaller adenomatous polyps. However, polypoid forms of hypertrophic gastritis, which have much in common with polypoid gastric tumors, usually are recognizable only on gastroscopic examination.

SPLENIC ANEMIA AND HEPATIC CIRRHOSIS

Painless, severe and recurrent hemorrhage and the symptoms engendered by severe anemia may be the sole complaints of a patient who has splenic or hepatic disease, or both. That some members of the profession are quick to jump to the conclusion that a hemorrhage is the result of a gastro-duodenal ulcer, even in the absence of symptoms of pain or indigestion, is sometimes exemplified by the fact that an enlarged spleen remains undiscovered until late in the course of the disease. Under the circumstances there should be little difficulty in making a proper diagnosis. In cases of hepatic cirrhosis without obvious increase or decrease in the size of the liver and without frank signs of portal hypertension or icterus, considerable difficulty may be encountered, especially in the early stages. In doubtful cases, tests of hepatic function, roentgenographic examination of the lower portion of the esophagus for varices, or laparotomy, are usually necessary in order to establish the diagnosis. Cases 4 and 5 are illustrative of this group. Comparatively, such lesions fortunately are infrequent causes of hemorrhage. Rivers and Wilbur (3), in a review of cases of hematemesis encountered in the clinic over a period of two years, found that only in about 9 per cent of the cases was hemorrhage diagnosed as being due to causes extraneous to the gastro-intestinal tract; such were principally due to various forms of blood dyscrasia, splenic disease and hepatic cirrhosis.

Case 4. A man, twenty-five years of age, registered at the clinic January 10, 1938, because of "repeated hemorrhages from the stomach and bowels." In 1934, four years previously, he had experienced his first hemorrhage. This was characterized by severe hematemesis on two successive days, followed by the passage of tarry stools for six days. Although he had not experienced abdominal pain or indigestion prior to, during, or since these hemorrhages, he was treated at that time for gastric ulcer. Six months later he had noticed tarry stools for four days. Then, for a period of two years, he remained entirely free of hemorrhages. In September, 1936, he had two massive hemorrhages, chiefly hematemesis, which resulted in syncope and shock, and repeated transfusions were necessary. In December, 1937, he had experienced melena for several days, which had been preceded by weakness, and by tachycardia on exertion. There were no symptoms or signs suggestive of hemophilia, purpura hemorrhagica, or other dyscrasias.

Physical examination showed that the spleen was enlarged. The patient had been totally unaware of this. The spleen extended for four fingerbreadths below the left costal margin. The concentration of hemoglobin was 62 per cent; erythrocytes numbered 3,510,000 and leukocytes, 5400, per cubic millimeter of blood. Differential count and morphologic examination of a blood smear did not reveal significant abnormalities. Roentgenoscopic examination of the stomach and duodenum gave essentially negative results, but varices were discovered in the lower half of the esophagus. Tests of hepatic function and estimation of serum bilirubin gave essentially normal results. The von den Bergh reaction was indirect. A diagnosis of splenic

nnemia with profuse hemorrhages from esophageal varices, was made.

A splenectomy, including ligation of the coronary vein and a Tnlma-Morison type of omentopexy, was done in January, 1938. This operation was preceded and followed by repeated transfusions of blood. The liver, gall bladder, stomach and duodenum were examined carefully at the time of the operation and were found to be normal. Since this operation the patient has enjoyed much better health than formerly, but he has had two mild hemorrhages after violent physical exertion, against which indiscretion he had been cautioned repeatedly.

Case 5. A man, thirty-two years of age, first entered the clinic January 7, 1935. In November, 1934, he had experienced a sensation of weakness and dizziness and soon thereafter had passed tarry stools, which recurred on three successive days. He stated that he "almost passed out." A month later he had a more severe hemorrhage, without syncope; it caused acute anemin and required two transfusions of blood. Otherwise, he had had no complaints of a gastro-intestinal nature. Except for evidence of moderate anemia, the physical examination gave essentially negative results. The concentration of hemoglobin was 70 per cent and erythrocytes numbered 3,860,000 per cubic millimeter of blood. The platelet count and the coagulation time of the venous blood were within normal limits. Other laboratory investigations, which included roentgenoscopic examination of the stomach and duodenum, tests of hepatic function, examination of the feces for blood when he was taking a meat-free diet, and examination of the esophagus for varices disclosed no abnormality. Cholecystographic examination, however, revealed a poorly functioning gall bladder. A similar result was obtained on examination several months prior to entering the clinic. Surgical exploration of the gall bladder, liver, pancreas and upper portion of the digestive tract was recommended but was refused.

The patient was re-examined at the clinic on June 21, 1935, because of melena of a week's duration which occurred two weeks previously. The roentgenologic findings were identical with those of the previous January.

The patient did not come under our observation again until after a lapse of four years. In the meantime, he had experienced about twelve more hemorrhages, seven of which were massive. Syncope was associated with three of them. He had been treated on the basis of a duodenal ulcer and alimentary allergy, but bleeding had occurred during active treatment for both conditions, on various occasions. Gastrosocopy had been performed by a gastroscopist of international reputation on six different occasions up to very recently. The results of these examinations were essentially negative. Unusual physical and mental exertion, exposure to cold, and infections of the upper portions of the respiratory tract predisposed definitely to bleeding. Evidence of steatorrhea of progressive severity has been present for eighteen months. The spleen also was found to be enlarged recently. Examination at this time, at the clinic, disclosed esophageal varices, a high grade of retention of bromsulfalein, moderate splenic enlargement, an excess of fat in the feces, and a nonfunctioning gall bladder. Roentgenographic examination of the stomach and duodenum gave negative results. The serum bilirubin was within normal limits but the van den Bergh reaction was direct. A diagnosis was made of recurrent massive hemorrhage from esophageal varices incident to portal cirrhosis, and highly probable, associated chronic cholecystitis and chronic pancreatitis.

LATE POSTOPERATIVE SEQUELAE THAT GIVE RISE TO HEMORRHAGE

Hemorrhage that occurs several months or years after an operation for chronic ulcer, especially duodenal ulcer, constitutes one of the most perplexing diagnostic and therapeutic problems that the physician

encounters. Lesions that give rise to such hemorrhage are frequently otherwise symptomless by virtue of certain favorable conditions effected by the operation, or because the lesions are of a superficial character, confined to the mucosa, whether such lesions are localized or diffuse.

The diagnostic significance of late postoperative hemorrhage, whether silent or otherwise, is partly dependent on whether the original lesion was of the bleeding type or not. Hemorrhage that occurs after gastrojejunostomy for hemorrhagic duodenal ulcer usually implies that the bleeding had its source in the original lesion, as the result of reactivation, whatever the cause. Under such circumstances the hemorrhage is usually unassociated with any other symptoms, unless a jejunal ulcer also might have developed in the meantime. On the other hand, hemorrhage that occurs for the first time after gastrojejunostomy or after a Billroth II type of operation for a nonhemorrhagic duodenal ulcer, is usually indicative of the formation of a lesion, an ulcer or gastritis, at some site other than the original one. Case 6, while an unusual one, is illustrative of the latter type. Similarly, late hemorrhage that occurs after any operation in which the original ulcer was removed, implies the formation of a new ulcer, the presence originally of multiple ulcers, one or more of which was overlooked, or postoperative gastritis. As roentgenologic diagnosis of postoperative lesions which may give rise to hemorrhage is often very difficult, gastroscopic examination always should be carried out whenever there is any reasonable doubt about the diagnosis.

Case 6. A boy, seventeen years of age, first entered the clinic on January 9, 1928. He had had a gastrojejunostomy for congenital pyloric stenosis, elsewhere, in 1911, when only five weeks old. In May, 1926, fifteen years later, he had experienced a sudden collapse and anemia. In August, 1926, he had had massive hematemesis and melena, followed by syncope. At that time the concentration of hemoglobin was 25 per cent (Dare). Analysis of the gastric contents showed an absence of free hydrochloric acid, and roentgenographic examination of the stomach, the stoma and the duodenum did not reveal any abnormality. The diagnosis was late postoperative gastro-enteric hemorrhage of undetermined origin. On his return home, a local surgeon submitted the patient to operation, at which time he performed a Billroth II type of pylorotomy (January, 1928). The patient consulted us again on June 3, 1935, because of recurrent attacks of severe melena, which had been present periodically since 1930. Roentgenoscopic examination of the stomach and anastomotic region after resection showed nothing abnormal. However, operation was advised and on June 17, 1935, the operation was performed at the clinic and cystic polypoid hyperplasia of the mucosa of the stoma was found. The gastrojejunostomy was disconnected, the peri-anastomotic tissues were excised and an end-to-side anastomosis of the stomach and duodenum was done. The patient has enjoyed good health since the operation.

DIAPHRAGMATIC HERNIA

A number of observers, notably Gardner (4) and Boek and his associates (5), have pointed out that diaphragmatic hernia may be the cause of gross gastric hemorrhage or of secondary anemia of varying degrees of severity. One of our patients, who was eventually found to have such a hernia complained only of dyspnea and of edema of the lower extremities, which were the direct result of severe secondary anemia of which the patient was unaware. The bleed-

ing is usually attributed to venous congestion of the gastric mucosa caused by compression of the stomach by the diaphragmatic muscles. Harrington (6), who has repaired surgically many of these hernias, has been of the opinion that the bleeding has its origin in traumatic erosion or ulcer of the mucous membrane caused by the forceful pressure exerted during the attacks of vomiting, on the large, distorted and congested stomach, and by the trauma caused by the hernial ring as the stomach is forced in and out of this opening. This erosion may be superficial, or in cases of long standing, may become definitely ulcerated from repeated trauma. Reduction and repair of the hernia results in prompt healing of the traumatized mucous membrane and cessation of hemorrhages.

ULCER OR NEOPLASMS OF THE SMALL BOWEL

Ulcer or neoplasms of the small bowel, admittedly rare, or ulcer in a Meckel's diverticulum, may give rise to painless melena. In all obscure cases of hemorrhage, it is important to examine the small bowel roentgenologically even in the absence of pain or obstructive symptoms, if the investigations up to that time have failed to disclose any lesion in the stomach or duodenum. Recurrent melena of children or young adults, without gastric disturbances, always should raise the suspicion that a bleeding intestinal lesion is present, especially an ulcer of a Meckel's diverticulum. A history of hematemesis would exclude the presence of a lesion below the level of the duodenum or duodeno-jejunal angle. Case 7 is an example of a "silent" bleeding tumor of the small intestine.

CASE 7. A man, forty-three years of age, entered the clinic January 12, 1939. For three and a half years prior to this he had complained of almost daily belching and mild heart burn, the latter appearing soon after meals. In 1936, he had experienced an attack of nausea and prostration, followed by melena in forty-eight hours. The latter persisted for a period of eight days. Melena recurred in June, September and December, 1938. He had experienced vague gastro-intestinal disturbances, which were relieved by a bland diet and antacids. Roentgenologic examination disclosed a crescentic defect of the upper portion of the jejunum, characteristic of submucosal leiomyoma. There were also signs of ulceration of the central portion of the tumor. On February 4, 1939, a partial jejunectomy was done for a leiomyoma that measured 4 by 4 by 3 cm., with a region of ulceration of overlying mucosa 4 mm. in diameter. The patient had an uneventful convalescence.

UNDETERMINED CAUSES

A constant challenge and source of humility are those instances of gross hemorrhage coming under our purview from time to time in which it is impossible to determine satisfactorily the cause of the condition. In the presence of pain and other disturbances strongly suggestive of ulcer, gross hemorrhage would point strongly to organic disease, in all likelihood, an ulcer or gastritis, in spite of the absence of roentgenologic evidence of a lesion. Berkman (7), in a study of cases of concealed gastro-intestinal hemorrhage encountered in the clinic, has been of the opinion that the largest number of cases of unexplained hemorrhage is due to duodenal ulcer or regions of duodenitis. Of eighteen patients who had experienced hemorrhage of undetermined origin, who underwent exploratory operation in the clinic, Berk-

man (8) reported that the cause of the hemorrhage was determined in ten, seven had duodenal ulcers, one associated with gastric ulcer, one had a fibrosarcoma in a Meckel's diverticulum, one had an annular carcinoma of the upper part of the jejunum, and one had a questionably malignant lesion on the lesser curvature of the stomach. Infrequently, carcinoma of the ampulla of Vater is responsible for obscure instances of melena.

In the complete absence of pain or dyspeptic symptoms, superficial erosions, acute ulcers, focal or diffuse gastritis, or causes extraneous to the stomach or duodenum, as illustrated by cases 4 and 5, would play a probable role. It is reasonable to assume that gastroscopic examination, undertaken soon after a hemorrhage has occurred, might supply information that would be lacking later, owing to the evanescent nature of some of the superficial mucosal lesions which can give rise to hemorrhage. It would not be the better part of wisdom to urge surgical exploration in cases in which lesions are painless in order to establish a diagnosis, unless there was a reasonable threat of malignancy, or unless the hemorrhages were excessive and recurred at frequent intervals. Under any circumstance, it is essential that patients who suffer from bleeding of undeterminable cause be kept under observation, as developments of a tangible nature often take place sooner or later. It was pointed out early in this article that hemorrhage may be the initial sign of duodenal ulcer months or years before other characteristic subjective symptoms or objective signs appear.

Disorders of metabolism, toxemias and avitaminosis, frequently difficult of recognition and appraisal, at times must be important etiologic factors in obscure instances of hemorrhage. In recent years various writers have ascribed to deficiency of Vitamin C a significant role, not only in cases of ulcer but especially in those of hemorrhagic ulcer. Numerous studies in nutrition have shown that in sub-clinical states, Vitamin D deficiency is very prevalent. Goldsmith and Ellinger (9), on the basis of their studies, have urged caution before attributing to ascorbic acid the role of an etiologic factor in any pathologic state. They are of the opinion that such depletion of the Vitamin C contained in the tissues may be only a concomitant finding or a result rather than a cause of the disease under consideration. Although vitamin deficiency may play an important role in capillary bleeding, I doubt that it has any importance in bleeding which is the result of arterial erosion.

Absence of pain in these cases of hemorrhage, from one cause or another, naturally raises the question of individual sensitivity. Determination of the degree of sensitiveness to pain by Libman's (10) simple method was not done routinely in the cases under consideration, so that definite conclusions from this standpoint cannot be drawn. Crohn's (11) observations in cases of gastric and duodenal ulcer led him to believe that insensitive individuals may experience the most severe complications because such persons are deprived of one of the most important of nature's defense mechanisms, that is, the ability to feel and to react to visceral pain. In his group of cases of ulcer complicated by hemorrhage, 40.8 per cent were comparatively insensitive, in contrast to a normal of 12 per cent. To what extent we have been misled in this respect is debatable, because the validity of Libman's procedure

still awaits general acceptance and confirmation. Other factors bearing on individual sensitivity to visceral pain undoubtedly also play an important role, if not a dominant one, such as the nature of the underlying lesion, the depth of the lesion, the nature and degree of the resulting visceral dysfunction, and the extent of direct involvement of nerves or peritoneal structures. For example, one would not anticipate pain in cases of uncomplicated hepatic or splenic disease. Superficial lesions, such as those comprising the gastritides, frequently are painless. The paucity of symptoms in association with benign tumor can be attributed to the absence or paucity of gastric secretory, spastic and motor disturbances, as has been pointed out by Moore (12).

SUMMARY

Silent gastro-intestinal hemorrhage may be caused by various lesions that are intrinsic or extrinsic to the digestive tract. One of the commonest causes is chronic duodenal ulcer, or duodenitis. In 1.5 per cent of 1089 verified benign ulcerative or inflammatory duodenal lesions, hemorrhage was the sole sign. In another 2.2 per cent, or in a total of 3.7 per cent, painless hemorrhage constituted the outstanding, almost exclusive, manifestation of the disease. Painless hemorrhage may be the initial sign of a duodenal ulcer, occurring months or years before the usual symptoms are manifested.

Other lesions that frequently give rise to painless hemorrhage are chronic gastritis, benign gastric tumor, splenic anemia, hepatic cirrhosis, jejunal ulcer, gastrojejunitis and postoperative gastritis. Of less importance, because of their comparative infrequency, and yet, of great clinical interest as the cause of silent hemorrhage, are para-esophageal hernia, ulcers or neoplasms of the small intestine, and ulcer of Meckel's diverticulum.

For patients who are subject to recurrent hemorrhage from time to time, eventual developments may be such as to make possible a satisfactory diagnosis and the institution of the proper treatment. In some instances, the cause of the hemorrhage is not ascertained even after exploratory laparotomy. Whatever the cause, whether intrinsic or extrinsic to the digestive tract, unusual physical or mental stress or alcoholic indiscretions predispose to bleeding and should be guarded against by the patient.

Whether the absence of pain is due to individual nonsensitivity or to certain anatomic and physiologic factors, such as the depth of the lesion, the degree of resulting visceral dysfunction, the extent of direct involvement of nerves or peritoneal tissue, or to a combination of these factors, has not been definitely determined.

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DISCUSSION

DR. JULIUS FRIEDENWALD (Baltimore): I should like to discuss Dr. Andresen's paper.

There is no problem in therapeutics which will require more careful consideration nor cause greater anxiety to the clinician than the treatment of persistent or massive gastric hemorrhage. It may require the combined judgment and effort of both internist and surgeon to decide upon the best plan of treatment.

Prophylactically much can be accomplished. As soon as tar-colored stools are noted, the patient must be confined to bed under strict dietetic regulation, until bleeding ceases. Only by such precautions can massive hemorrhage sometimes be averted.

We are in accord with most of the conclusions arrived at by Dr. Andresen. Ever since Clement Jones presented his paper in 1921 before this Association, on his observations on hematemesis in which he called attention to the beneficial effects of gelatin in this condition, we have utilized gelatin mixtures in our clinic in the treatment of gastric hemorrhage with most satisfactory results.

On account of nausea and vomiting, this may be the only remedy that can be retained for the first day or two following the hemorrhage. Aside from the use of morphia and absolute rest, a soft diet is given for nine or ten days, and gradually enlarged to a regular and balanced diet in a manner much like that recommended by Dr. Andresen. Transfusions may be required at any time and the necessary grouping should be determined at the very beginning in order to be in readiness should the occasion arise.

In instances of massive hemorrhage with blood counts below two million and hemoglobin below 40 per cent, transfusions have been invaluable. We have found that small transfusions of 200 to 250 cc. of blood, repeated, if necessary, at intervals of three to five days, have been extremely helpful in stimulating blood formation as well as in controlling hemorrhage. When the stomach is distended with food remnants, fluids, or coagulated blood, lavage with warm water is a helpful procedure, but in our experience should not be resorted to unless considered absolutely essential.

We have not observed that the so-called coagulants have been of decided help in controlling the hemorrhage in any of our cases.

From our experience we are convinced that blood pressure readings play a far more important role in the prognosis of gastric hemorrhage than the low hemoglobin readings, although the latter often falls to the low value of 35 with subsequent complete recovery. A red cell count of two million or less is not unusual.

A fall in blood pressure to from 80 to 85 systolic without being followed by a rise, is always an alarming sign. A rise, however, is often indicative of a cessation of the bleeding. As soon as hemorrhage has been overcome, iron in the form of iron and ammonium citrate should be administered in large dosage, and it is now known that iron absorption is far better when alkalization is omitted.

As the result of this plan of treatment which in the main resembles that of Andresen and even Meulengraecht, our mortality from gastric hemorrhage has been greatly reduced and the need of surgical intervention from this cause has fortunately become far less frequent.

We are certainly indebted to Dr. Andresen for his timely and most valuable paper.

DR. T. GRIER MILLER (Philadelphia): Mr. President and Members of the Association: I shall limit myself

largely to a discussion of Dr. Blackford's paper. He was good enough to send me a copy of it and, therefore, at some leisure I have been able to consider his and Dr. Cole's data on the mortality in hemorrhage from peptic ulcer. The data have been carefully analyzed, and their presentation should lead to clearer thinking about this very important subject, perhaps to a better selection of cases for surgery and eventually to a more satisfactory basis for the evaluation of various types of medical therapy.

Very properly Dr. Blackford has stated his criteria for the inclusion of cases in his group. I perhaps should point out that his exclusion of those patients who have anastomotic ulcer and of those who have moderate degrees of hemorrhage tends to increase his mortality. On the other hand, I wish to point out that he also excludes patients dying of post-operative complications after hemorrhage and that such exclusion tends to decrease his mortality rate. On that basis I question his right to solve his mortality for comparison with the data of most other authors.

As a matter of fact, comparisons of the data from various clinics on this subject is exceedingly difficult, if not impossible, not only because of differing objective criteria but also because of varying judgments as to the severity of the hemorrhage itself. Dr. Elsom and I, however, during last year carefully reviewed our own and others' data and have reported the results. We found that mortality after medical therapy ranged from zero to 25 per cent; the surgical mortality from 6 to 100 per cent. In all we obtained data on 6226 cases of grossly bleeding ulcer. Of those that had been treated medically, 8.7 per cent died; 28 per cent of those that had been treated surgically. Putting the two groups together, we found that 10 per cent of all the grossly bleeding ulcer cases had died. Dr. Blackford's total figure was only 11 per cent, which isn't very different, you see, from the average for all reported cases.

I was particularly interested in Dr. Blackford's references to the age incidence in the mortality from bleeding ulcer. As you noted from his chart, he had no patients die under forty-five. He had six die after forty-five. He is inclined to feel that the mortality is rather negligible under the age of forty-five; so does Dr. Cronin and so does Dr. Allen of Boston. Perhaps they are all right, but I should like to say that in our personal series of only sixty-eight cases we had a higher mortality in the patients under forty-five, namely, 14.6 per cent, as against 11 per cent in those patients who were more than forty-five years of age. The ages of our six cases under 45 years were 20, 28, 31, 39, 44 and 45.

I should also like to call attention to the fact that Dr. Blackford excluded three cases from his fifty-seven, two because they had post-operative complications, and one because an anastomotic ulcer was present; it happens that all those three were under forty-five years of age. So if we had included them, he would have had a 10 per cent mortality under forty-five. I wonder if he shouldn't at least have included those patients who died of post-operative complications. After all, weren't those patients operated on because they would otherwise have died, and did not the complications after operation develop because those patients' general condition was markedly impaired as a result of prolonged bleeding? If so, I think they should have been included.

I can't dispose so readily as Dr. Eusterman of the vital statistics data, but I should like to know about similar data from other public health departments.

DR. SIDNEY PORTIS (Chicago): I do not wish to prolong this discussion but I wish there were a rule of thumb by which we could handle all of these cases. The patient who intrigues me most is the one who has a massive hemorrhage associated with duodenal ulcer. This type of hemorrhage is very frequently associated with an eroded pancreoduodenal artery, and it should be suspected in a patient who has a known history of duodenal ulcer

and has a profuse massive exsanguinating hemorrhage. I think the sooner that these patients get to the operating table the more likely it will be that their lives will be saved.

I have seen enough of this evidence at the necropsy table to impress upon me the futility of medical treatment in trying to control this type of hemorrhage. The only treatment is immediate surgical intervention with adequate transfusions and to ligate the vessel.

The other point that occurred to me during the course of these papers was that in patients with bleeding duodenal ulcer, it is most important during the course of medical management, to keep the pylorus in a state of partial relaxation, and I think this can be accomplished by a sufficient amount of atropine, which will allay active peristalsis somewhat and tend to permit a more rapid healing of the bleeding ulcer.

DR. J. RUSSELL VERBRYCKE, Jr. (Washington, D. C.): Mr. President: My treatment of ulcer is very much like my politics. I am a hidebound conservative. I had an occasion to look over the records just before I left, and I have one slide I should like to have shown while I am making these several remarks.

I don't believe that the age incidence is as important as the diseases which naturally come with age; for instance, in looking over the mortality rate, I find that massive hemorrhage, not just gross hemorrhage, gave us a mortality rate of 3.1 per cent from ulcer, but when all massive hemorrhages were included, that is, cirrhosis, cancer, syphilis, we went to 11.9 per cent; in other words, our mortality rate from conditions which were not ulcer, is over three times that of ulcer cases.

I agree with the statement that the vital statistics are not very helpful, and I believe that many of the cases of hemorrhage reported as being due to ulcer without any studies having been made before the patient died, were probably not ulcer at all.

There are several statements that I want to make here. The first is about the time for operation, time for operation if the patient is seen not to be getting well under medical treatment. If that is true, the time for operation is after his respirations have ceased, because it doesn't make any difference if the patient gets practically pulseless. That is part of the reason for the hemorrhage stopping, and the main thing is not to get panicky, no matter how bad the patient gets, and not to rush from one thing to another.

The same thing can be said about transfusions. I say "never transfuse," that is, during the active treatment of the ulcer. Never add water. A patient may be dehydrated but don't pay any attention to that during the acute stage.

If anything has to be done, certainly small hypodermoclyses are better than anything else, but no transfusion and no intravenoses of any kind.

Dr. Andresen doesn't like ice. I use ice and still stick to it. I can find fault with him—I don't like the iron in the stomach. I think probably one would irritate us much as the other, that is if either does harm. I would prefer to give my iron later on with hypodermics rather than introduce it into the stomach.

I noticed that our highest mortality came from post-operative marginal ulcers, from ulcer with cancer, cancer and syphilis, cancer with obstructions, plain cancer, cirrhosis, and Banti's.

DR. RALPH C. BROWN (Chicago): I should like to add my voice to the conservatism Dr. Verbrycke has just expressed and also note certain factors which I feel greatly influence the prognosis as well as the treatment of massive hemorrhage in peptic ulcer.

We are all influenced by the personal experience we have had when it comes to forming an opinion as to how likely a given patient is to die and what to do about it, and as I look back over the years I find that when faced with the emergency of a serious hemorrhage, I have

anxiety as to the outcome in only two groups of cases, namely, massive hemorrhage in the older individual who shows evidences of a marked degree of arteriosclerosis and the far larger group of cases in which the history of pain during the midnight hours indicates the presence of pyloric obstruction with continued gastric secretion or the continued night secretion which may accompany a large, chronic, deep-seated gastric ulcer.

With the massive hemorrhage patient lying before one the immediate objective is, of course, clot formation, but a blood clot is just as readily digested by gastric juice as egg albumen. The patient with no pyloric obstruction or continued secretion and with fairly good arteries may very well be left alone and nine times out of ten nothing further will happen to him. But no matter how effective the daytime management may be, if the forming blood clot is exposed to the digestive action of an excessive continued night secretion, the presence of which may be determined by aspirating with a Rehfuß tube, then hemorrhage is extremely likely to recur.

Therefore my plea is that we should keep in mind the necessity of recognizing, when possible, the existence of pyloric obstruction and continued secretion and of taking appropriate measures to safeguard the patient. The crux of the matter is effective acid neutralization, thus preventing digestion of the clot. Meulengraft achieves his low mortality figures by using frequent feedings and alkalis. If appropriate measures are also used during the night hours as well—and there are various ways in which a continued secretion may either be removed or neutralized—cessation of hemorrhage is likely to result. After forty-eight hours have passed without sign of recurring hemorrhage the patient will be relatively safe.

DR. RUDOLF SCHINDLER (Chicago): I was glad that Dr. Eusterman has pointed to the frequency of hemorrhage from painless ulcer. We have become aware of this fact especially since in the clinic of Dr. Palmer we examine our ulcer patients at very short intervals, intervals of two weeks or four weeks, gastroscopically as well as at X-ray. We see that the patient comes telling that he is feeling fine and we see a recurrence of his ulcer, and then, in quite a few cases it has occurred that some weeks later the first painless hemorrhage occurred.

I remember especially two cases of resected stomach in which the patient came back telling that he was feeling fine and gastroscopically I saw a very definite marginal ulcer in both cases, and both cases, two or three weeks later, had a gross hemorrhage, and in one of the patients a short time later I could see the thrombus in the midst of the ulcer and still the patient had no pain.

I observed three cases of myoma gastroscopically, and all three were referred because of gross gastric hemorrhage.

DR. JOHN L. KANTOR (New York): May I ask a question of Dr. Blackford? If every one of the operated patients in the older group died, why does he still recommend surgery in these older patients?

DR. FRANKLIN HOLLANDER (New York): Mr. President, I would like to introduce a very academic note into this discussion. For the last three years I have been sitting on the sidelines at our hospital and here at the meetings of the Association, listening to discussions on hemorrhage with a great deal of interest in this controversy.

Not being a medical man myself, I probably bring a little less bias to bear in my analysis of this problem than most of you clinicians do, and I have observed this very interesting thing: A discussion usually starts out with very well defined statistics. I think all three of the papers which we are discussing now are statistical. You present numbers as evidence of this or that or the other situation. Before the discussion has gone along very far, however, you are discussing your own clinical impressions on the situation. These clinical impressions arise in part from a

diffuse interpretation of what you observe at the bedside, a thing about which nobody can argue with you, and in part from a non-mathematical interpretation of the numbers which you put down on paper or on your lantern slides.

It seems to me that a great deal of your discussion would be simplified or made wholly unnecessary if you took your statistical data more seriously and consulted a biometrician about your fundamental facts before you attempted to organize your clinical ideas on these questions. I am fairly well convinced from my experience at our hospital in New York that a great many of the differences between groups of data with which you are dealing are statistically non-significant for various reasons; that you are arguing about differences which do not exist, and which appear in your studies only because of errors in what we call sampling. You pick a group of fifteen, or twenty five, or maybe even fifty cases in a particular situation. You get a certain numerical measure of your clinical result. If, in your own hospital or private practice, you were to pick a similar group of fifty, you might well find a markedly different result—even though your working conditions appeared to be the same. How then can you justify a comparison of your own results with those of others, unless they have first been subjected to vigorous statistical scrutiny. To base extensive arguments on such differences, without adequate statistical analysis of your data, is wasting a good deal of your own time and energy.

DR. A. F. R. ANDRESEN (Brooklyn, N. Y.): In regard to statistics, I agree entirely with the criticism expressed. I dislike statistics because they can so readily be used to prove anything the speaker desires to prove.

Much stress has been laid upon the presence of a protective mechanism in regard to vitamins. Our observations in regard to vitamins are in agreement with these findings as noted in the body of the paper. As a matter of fact, the whole treatment for hemorrhage which I have outlined is based on the fact that nature has provided a protective mechanism which acts as soon as an ulcer begins to bleed and which must not be interfered with to get the best results. I have pointed out that the general weakness, the diminished blood volume and reduced blood pressure are important factors in permitting formation and organization of a thrombus in the bleeding vessel and that it is unphysiological suddenly to increase blood volume and pressure by means of transfusion or other intravenous injections. Iron medication has been found usually unnecessary because blood regeneration takes place naturally and rapidly without it. Even late transfusions, formerly recommended, have been found rarely necessary or of value.

DR. GEORGE B. EUSTERMAN (Rochester, Minn.): This symposium has been an instructive one. Discussion relative to treatment can readily terminate in a "free for all" because there is such a difference of opinion as to what constitutes the most effective procedure. Doctor Andresen's method, like anything he advocates, has its excellent points. The majority of the reports bearing on the results of the Meulengraft regimen or its modifications, are highly favorable to it, yet some discriminating clinicians are not ready to accept it and in fact feel that it is contraindicated under certain circumstances.

Knowing Doctor Hollander as I do, I feel sure that he did not mean to give the impression that statistics are useless and misleading. When scientifically compiled they are essential to medical progress. We have ourselves appreciated the importance of a full time statistician. The necessity for scientific statistical surveys is seen with reference to the subject under discussion. Data bearing on mortality from gastro-enteric hemorrhage are in a hopeless muddle, as you all know. This is largely due to the fact that calculations are based on all degrees and types of bleeding. A start in the right direction can be made by confining our observations to individuals who had

massive hemorrhage, the criteria for which have just been laid down by Doctor Blackford.

DR. JOHN M. BLACKFORD (Seattle—Closing): The discussion of the value of vital statistics has interested me much, because I am fully aware of the difficulties one may get into in the interpretation of statistics.

In replying to Dr. Eusterman's remarks, I would state that I agree with him fully in principle. Nevertheless, I must state again that the clinical records of these 55 deaths taken from the Bureau of Vital Statistics were reviewed by us almost as carefully as we might have reviewed the records of Dr. Eusterman himself. If I had gone back to Dr. Eusterman's records of such cases as I did in the instances taken from Vital Statistics, I would feel that I had approximately accurate and final information. It would make little difference where the cases came from if the records were fairly complete; for hospital records, whether from Seattle or from Rochester, must be more or less accurate:—50 of our 55 patients recorded in Vital Statistics died in hospitals.

We happen to have in Seattle three excellent pathologists who did postmortem examinations on 43 per cent of the Vital Statistics cases. I think this audience knows fully about the limits of clinical error in the diagnosis of the source of gastric hemorrhage; you know that with a clinical diagnosis of ulcer various authors estimate the error between 10 and 20 per cent. Certainly the maximum error in our cases should not be over 10 per cent, if 20 per cent is the maximum error, for the autopsy findings must be accepted in the 23 cases in which autopsy was done.

In 51 patients included in our series taken from Vital Statistics, chronic peptic ulcer was the only lesion; 49 of the 51 died above the age of 45 years. That ratio, whether

taken from vital statistics or from the Mayo Clinic or from Seattle, should be the same. We have shown by tabulation of all cases that the distribution by age is as stated.

Dr. Miller remarked on the larger mortality he has found in younger patients studied from Philadelphia records. I would strongly suspect that he has included surgical with his medical mortality, and that somewhere in Philadelphia we may have some surgical enthusiasts operating upon younger patients for massive hemorrhage.

Dr. Kantor has asked for the reason for operation. I apologetically stated that we had operated on some younger patients; and then remarked that we had lost two older patients following operation. The patients operated upon in our vital statistics series were all in the older group, and all were operated upon after waiting from one to three weeks. Such delay, in our experience (based on vital statistics experience and our own hospital experience) has been almost always fatal.

I feel most emphatically that the evidence shows that massive gastric hemorrhage from peptic ulcer occurring between the ages of 50 and 70 carries a mortality rate of approximately 30 per cent; or if the mortality percentage is based on all active gross hemorrhage from peptic ulcer in this older group, then the figure is approximately 15 per cent. Many of these fatalities should be spared by proper surgery. It seems to me that the tragedy of a massive hemorrhage from peptic ulcer in a person between 50 and 70 years of age must be compared with that of the hemorrhage from a ruptured liver or spleen. Serious hemorrhage from any of these sources seems to me an indication for exploratory operation. Certainly delay for many days after great loss of blood and then operation has resulted in terrific mortality. If operation is to be considered it should be done promptly after transfusion.

Some Unusual Gastro-Enterological Surgical Problems*

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ANY discussion of the diseases of the gastro-intestinal tract obviously centers about methods of treatment for the condition whether for functional or organic disease. Any method of management may be directed toward correction of altered physiologic or actual pathologic changes. The treatment of such recognized alterations from the normal, whether medical or surgical in their application, has been with few exceptions, accurately established and practiced by gastro-enterologists and surgeons. However, some pathologic processes have proved to be peculiarly unsuited to any form of direct attack such as surgery, principally because of poor results and because of the high mortality attendant upon any attempt at surgical management. Within the past few years the surgical treatment of such lesions of the gastro-intestinal tract heretofore considered inoperable has been made possible by virtue of improvements in surgical technique and of improvements in anesthesia. Certain highly technical operations designed for such problems have become justifiable because of an increasingly high

percentage of successful results and because of the lowered operative risk. Such surgical procedures to be justifiable, then, must be so planned and executed that one may offer the patient a better than reasonable chance of relief of distress, a distinct possibility of cure or at least a prospect of prolongation of life without disturbing gastro-enterologic symptoms and, above all, without prohibitive operative risk.

We will discuss in this paper some of the advances made in the surgical management of certain lesions of the gastro-intestinal tract. We wish to include in this group a plan for the management of large gastro-jejunal fistulas, the problem of total gastrectomy for malignancy of the stomach, a method of resection for carcinoma of the lower end of the esophagus, together with some unusual surgical problems of the duodenum and jejunum.

It is unnecessary to point out that such highly technical surgical procedures require not only considerable experience and technical ability on the part of the surgeon but also the collaboration of a skilled internist in the selection of cases. Boldness and skill must be tempered by sound judgment on the part of

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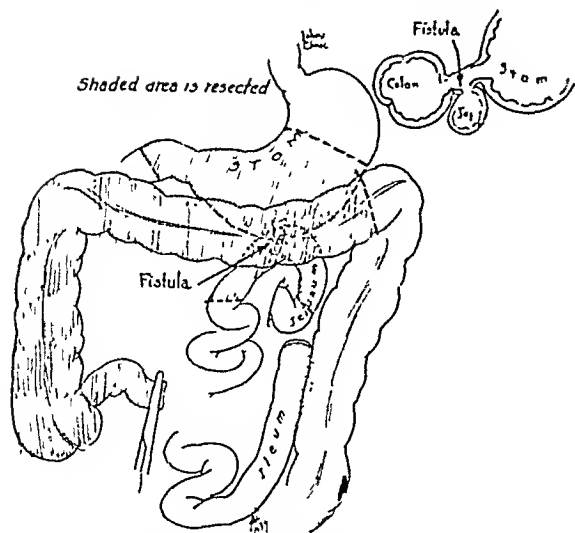


Fig. 1. Gastrojejunoceolic fistula. Method of surgical management, first stage of operation. Terminal ileum is divided and ends of bowel closed by inverting sutures. A lateral anastomosis is made between proximal loop of divided ileum and a portion of the colon distal to fistulous communication. The shaded area of stomach and intestine illustrates portion to be resected at second stage. Insert shows relationship of fistula to stomach, jejunum and colon.

both internist and surgeon and results must certainly justify the selection of cases. Rash surgery can hope only to discredit both and cannot be too vigorously condemned.

One of the most serious complications of gastro-jejunoostomy has been the occurrence of gastrojejunoceolic fistula. This lesion commonly follows the development of a jejunal ulcer at the site of the gastro-enterostomy stoma. The ulcer erodes and finally perforates into the adjacent transverse colon, producing a fistula leading from the colon into the jejunum and stomach. Many technical procedures have been proposed and performed to deal with such a fistula but all have been accompanied by an unduly high mortality because of the considerable risk of peritonitis from opening into a transverse colon filled with highly infective liquid contents. One of the most frequently employed methods of surgical management has been lysis of the fistulous tract, that is, to remove the tract and to restore normal gastro-intestinal continuity. This procedure not only carries with it the grave possibility of peritonitis but also, with restoration of normal gastro-duodenal continuity, reactivation of an old duodenal ulcer frequently occurs, the control of which still presents a serious problem.

The ideal surgical procedure, then, should include removal of the fistula as well as high resection of the stomach for control of the primary lesion, that is, the peptic ulcer which marked the beginning of the patient's difficulty. With this idea in mind, we have recently successfully employed a method embodying the safe removal of the fistulous tract together with high resection of the stomach. The operation has been performed in stages, with an interval of two weeks between stages. The first procedure consisted of division of the terminal ileum 6 inches from the cecum with closure by inversion of the ends of the proximal

and distal loops of ileum. An ileocolostomy, employing a lateral anastomosis is then made between the proximal end of the divided ileum and the transverse colon distal to the fistulous opening (Fig. 1). The purpose of this procedure is to permit emptying of the contents of the small bowel into the colon beyond the fistulous opening, reducing thus the colonic contents regurgitating into the stomach and at the same time establishing the fecal stream so that the colon with its contained fistula, jejunum and stomach may be resected in one block, thus avoiding peritoneal contamination.

Two weeks later a resection of the cecum with the small part of attached ileum, the ascending and transverse colon to a point beyond the fistulous communication, is carried out. Combined with this, high resection of the stomach is done and at the same time the affected jejunal loop is resected and an end-to-end anastomosis is made to reestablish jejunal continuity. These involved viscera are removed in one block without separating them. After resection of the stomach, the jejunal loop distal to this anastomosis is employed to form the gastrojejunal anastomosis (Fig. 2). The postoperative course has proved to be extremely uneventful; the patient improves rapidly and without the grave risk of a fatal peritonitis. We believe two factors influence the safety of such a method of surgical management; first, the change in the contents of

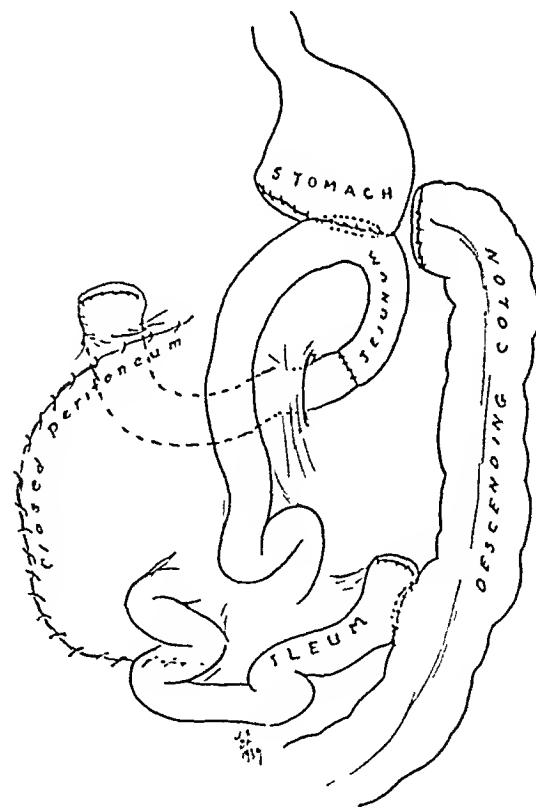


Fig. 2. Gastrojejunoceolic fistula; second stage of operation; operation completed. Right colon and transverse colon to a point beyond fistulous tract are resected. Involved jejunum is excised and end-to-end anastomosis of jejunum is done. A high resection of stomach of the Hofmeister type completes the operation. The involved viscera are removed in one block.

the transverse colon, resulting from sidetracking of the fecal current, thereby reducing the opportunity for peritonitis, and second, the production in the peritoneal cavity of a certain degree of immunity to colon organisms by the first operation. The second stage which may be an extensive procedure is not an insurmountable operation and can be performed without gross contamination of the peritoneal cavity, which is certain to occur if a functioning large bowel is opened as it must be in separating the jejunum or stomach from the colon by any plan which attempts to close the fistula into the colon by direct approach to it.

to the splenic flexure and then rapidly filled the stomach.

Operation was advised and carried out in two stages. The first stage of the procedure was performed through a right rectus incision at which time the terminal ileum was divided 6 inches from the cecum. The ends of the ileum were closed by inversion and a lateral anastomosis was made between the proximal end of the divided ileum and the descending colon. Convalescence from the first operation was uninterrupted. Two weeks later, through a high left rectus incision, the right part of the colon and transverse colon to a point well past the fistula were resected. The loop of involved jejunum was then resected and an end-to-end anastomosis of jejunum was done. The

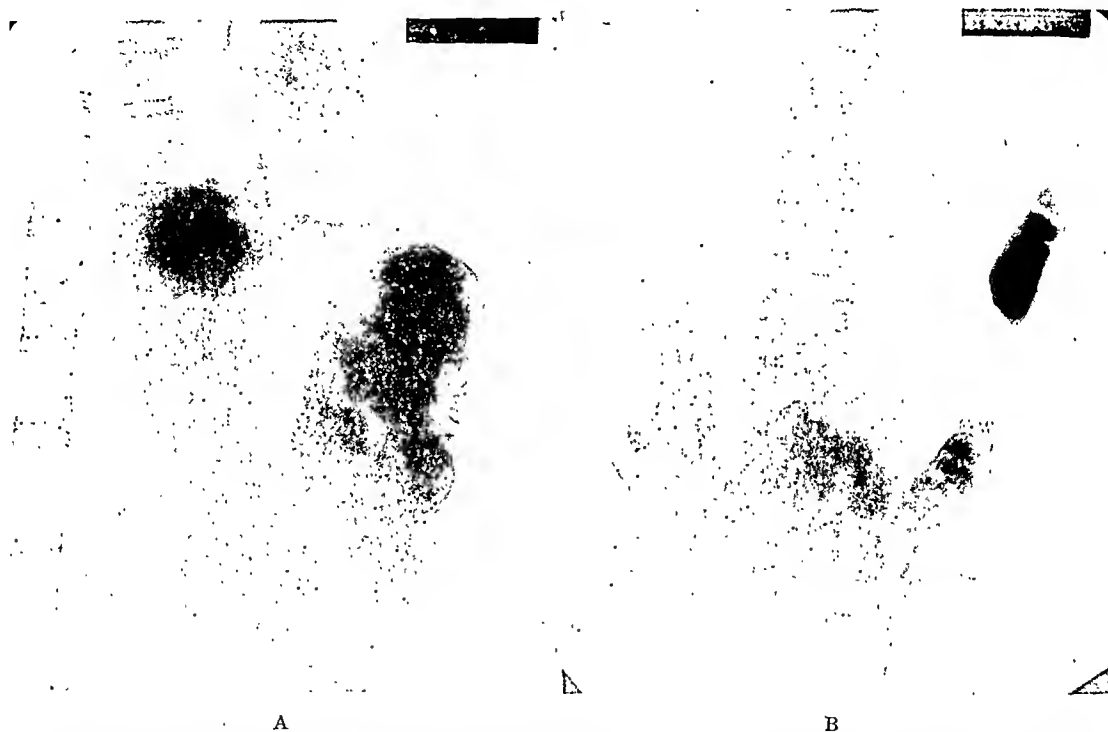


Fig. 3. Gastrojejunocolic fistula. Roentgen examination one year following operation. *a*, Roentgenogram of stomach following barium meal shows a gastric stump, one-fifth the size of the normal stomach. There is a good functioning stoma and little dilatation of the jejunum. *b*, Roentgenogram following barium enema. Barium is seen in the loops of ileum and the level of the ileocolic anastomosis is shown. Note that no barium goes beyond the splenic flexure of the colon.

The following case report is an example of the surgical management of gastrojejunocolic fistula.

CASE REPORT

A man, aged forty-three years, was first admitted to the clinic March 28, 1938, complaining of diarrhea and abdominal pain. He gave a history of acute perforation of a duodenal ulcer in 1918; gastro-enterostomy had been done elsewhere in 1929 for the relief of ulcer distress. Three years before admission to the clinic diarrhea was noted with seven to eight liquid stools daily. In the last year with continuation of diarrhea, undigested food was noted in the stools. Diarrhea occurred soon after meals. He also had some pain in the upper left part of the abdomen.

Physical examination revealed an essentially normal individual with the exception of rather marked undernourishment. A gastrojejunocolic fistula was readily demonstrated by fluoroscopic and roentgenologic examination; barium passed readily to a point 4 inches proximal

operation was completed with removal of four-fifths of the stomach and the formation of an anastomosis between the jejunum and the resected stomach.

Convalescence following this extensive procedure was entirely uneventful and the abdominal incision healed cleanly. The patient was discharged eighteen days after the second operation in excellent condition, with no dietary difficulties on a liberal regime. He was again examined one year after operation; he had gained 18 pounds, had no abdominal distress and had had no diarrhea (Fig. 3).

The problem of management of malignant lesions of the stomach by surgical measures is admittedly a perplexing one, yet the difficulty arises not so much from a technical viewpoint but more frequently as the result of delay in submitting patients with gastric lesions to operation. Naturally, this is a problem of early diagnosis which may depend upon a number of factors not directly under the control of the physician. Without

The following case report is an excellent example of a diffuse malignant process involving the whole stomach, for which total gastrectomy was done.

CASE REPORT

A man, aged forty-six years, was admitted to The Lahey Clinic, March 6, 1939, complaining of epigastric distress of one year's duration. This distress was frequently associated with nausea and vomiting and during the year he had lost 10 pounds. Anorexia and a tendency to fatigue were noteworthy symptoms. He had had roentgenologic examination of his stomach twice before admission to the clinic, without a definite diagnosis being made.

Examination revealed an undernourished individual with scaphoid abdomen. A tumor mass was readily palpated in the epigastric region. Analysis of gastric contents revealed absence of free hydrochloric acid and the presence of erythrocytes. Roentgenologic examination of the stomach demonstrated a large filling defect involving the medio of the stomach (Fig. 4). Barium passed rather quickly through the constricted region and the stomach was completely emptied in three hours. No evidence of metastasis could be found upon careful physical examination, and exploratory operation with resection of carcinoma of the stomach was advised.

Operation was performed March 23, 1939, at which time a stomach rigid from malignant infiltration of the walls was found, a typical linitis plastica. The entire stomach was involved and except for several small glands noted along the greater curvature, no evidence of metastatic spread of the tumor could be found. The stomach was completely removed and a loop of jejunum was brought anterior to the colon and anastomosed to the end of the esophagus (Fig. 5).

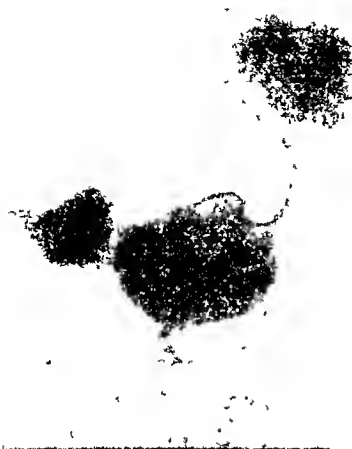


Fig. 4. Linitis plastica. Annular filling defect occupies the middle two-thirds of the stomach. Peristaltic waves are absent and defect is constant. Operation, total gastrectomy.

question, in recent years the field of gastric surgery as pertains to both ulcer and cancer has been greatly widened through improvement in technique. Problems of greater magnitude are successfully managed and a more aggressive attitude toward these lesions is justifiable upon the basis of results obtained. One need not necessarily speak in terms of cure of widespread malignant disease of the stomach but rather in terms of the alleviation of distress and prolongation of life which can be confidently predicted by surgeons experienced in gastric surgery. Total gastrectomy has been performed many times successfully and with satisfying results. Life has been prolonged, abdominal distress alleviated, with an ever decreasing operative risk, as well as in the vast majority of cases, an astonishingly low postoperative morbidity and freedom from postoperative distress.

One must admit that the number of patients upon whom a total gastrectomy is justifiable is limited; also, one cannot confidently determine from the clinical data and from roentgenologic evidence the patients upon whom total gastrectomy is possible. One can frequently suspect from data obtained by examination that if resection is possible the entire stomach must be removed. The gastric lesion which requires total gastrectomy involves most of the stomach and most frequently is the type described as a diffuse fibrocarcinoma of the stomach or linitis plastica. This tumor extends by infiltrating the walls of the stomach, producing a rigid diffusely thickened gastric organ, and can frequently be suspected from fluoroscopic examination of the stomach. This type of malignant disease is well recognized and the indications for complete removal quite well established.



Fig. 5. Roentgenogram following total gastrectomy. The barium outlines the esophagus and passes readily into the jejunum. The esophagojejunal anastomosis is shown at the level of the diaphragm.



Fig. 6. Carcinoma of cardia of stomach. Roentgenogram shows a bulky adenocarcinoma involving the cardia of the stomach and extending into the lumen of the esophagus. Operation, total gastrectomy.

Convalescence was uninterrupted and the patient was discharged eighteen days later, at which time he was able to take a satisfactory diet.

Total gastrectomy may also be employed with quite satisfactory results in other types of gastric malignant disease. One of us (1) has described complete removal of the stomach for leiomyosarcoma in a woman, twenty-seven years of age, who is alive and quite well one and a half years after operation. This tumor was of relatively low malignancy and had not spread beyond the walls of the stomach. We have (2) recently had another type of malignant tumor, a malignant lymphoma, which diffusely infiltrated the mucosa and the submucosa of the entire stomach, which did not penetrate the muscular layers and which stopped sharply at the duodenal and esophageal borders. This tumor occurred in a woman of thirty-two years. The stomach was thickened and rigid and in this case total gastrectomy was also successfully performed. The patient made a most uneventful recovery and was discharged from the hospital seventeen days after operation, upon a fairly liberal diet.

Another form of malignant involvement of the stomach which frequently lends itself quite satisfactorily to total resection is carcinoma of the cardia of the stomach. We have recently had two patients with large tumors of the cardia which had grown locally and which had not yet involved the diaphragm, liver, and other organs. These tumors were successfully removed by total resection, anastomosing the jejunum to the esophagus after the technic which we

have described (3). An illustrative case report of successful total resection of the stomach for a large carcinoma of the cardia is given below.

CASE REPORT

A man, aged fifty years, was admitted to the clinic November 25, 1938, complaining of difficulty in swallowing of thirteen months' duration. Swallowing was accompanied by soreness and pain in the epigastrium. The symptoms had increased in severity the last few months. He had lost 10 pounds. Roentgenologic examination done a month before admission showed delay in the passage of barium, which was interpreted as cardiospasm.

Physical examination at the clinic revealed an irregular mass involving the medial portion of the cardia of the stomach and extending into the distal portion of the esophagus (Fig 6). The remaining portion of the stomach and duodenal bulb were normal. Erythrocytes numbered 4,510,000 and the hemoglobin was 71 per cent.

At operation, November 29, 1938, a tumor mass was found which was as large as one's fist (approximately 8 cm. in diameter), and occupied the cardia of the stomach. No obvious gland involvement or distant metastasis could be demonstrated. Total resection of the stomach was carried out without difficulty and the esophageal stump was anastomosed into the lateral border of a loop of jejunum. The pathologist's report was adenocarcinoma of the cardia of the stomach with metastasis to two of fifteen lymph nodes.

The patient's postoperative reaction was extremely mild and he was discharged twenty days after operation upon a liberal diet and with no difficulty in swallowing.

One is not justified in refusing operation to patients with malignant disease arising in the cardia, and certainly with failure to demonstrate extension or metastasis, exploratory operation should be carried out in all cases with the hope of possible successful removal by complete gastrectomy. Whatever the findings, in the presence of obstruction to the lower end of the esophagus, some type of gastrostomy can be performed. Furthermore, as is discussed later, removal of the tumor even in the face of esophageal involvement is possible by means of a transpleural approach. It must be emphasized that the gastric malignant lesion inexorably progresses to a fatal outcome without surgical interference and any procedure which widens the scope of attacking the disease is a worthy one. In The Lahey Clinic, we have performed total gastrectomy in nineteen cases, with an operative mortality in five cases; two fatalities have occurred in the last ten total resections of the stomach done in the clinic.

It is of value at this point also to comment upon the importance of preoperative preparation in relation to morbidity and mortality which may follow such extensive technical procedures upon the stomach. For a period of more than two years all patients with gastric carcinoma have been prepared for operation by thoroughly washing the stomach with dilute hydrochloric acid the night before and in the morning immediately before operation. The bacterial counts as plated upon Petrie dishes have been reduced many times and in many cases, a sterile content of the stomach has been demonstrated.

The surgical removal of carcinoma of the lower end of the esophagus presents a somewhat more difficult problem than that associated with gastric malignant lesions. The question of successful removal is influenced by the inaccessibility of the lesion and by extension of the tumor to surrounding structures due to

delay in diagnosis and in advising treatment. Unfortunately, most of these patients are not referred to the surgeon until marked malnutrition has occurred as a result of obstruction of the esophagus. Ewing has drawn attention to the fact that carcinoma of the esophagus has a tendency to metastasize early because of the abundant blood and lymphatic supply and because of vigorous esophageal movements resulting from swallowing.

Very few cases of successful resection of this region, in which normal esophageal gastric continuity

cision, mobilizing the lower part of the esophagus in the thoracic cavity and exposing the stomach through a radial incision through the diaphragm (Fig. 7). After the cardia of the stomach is mobilized, the tumor is resected, together with a generous border of normal tissue on either side of the tumor. This necessitates removal of a portion of the cardia of the stomach as well as a portion of the esophagus. The stomach is then brought partly into the thoracic cavity to bridge the gap caused by removal of a segment of esophagus, and the divided end of the esophagus is

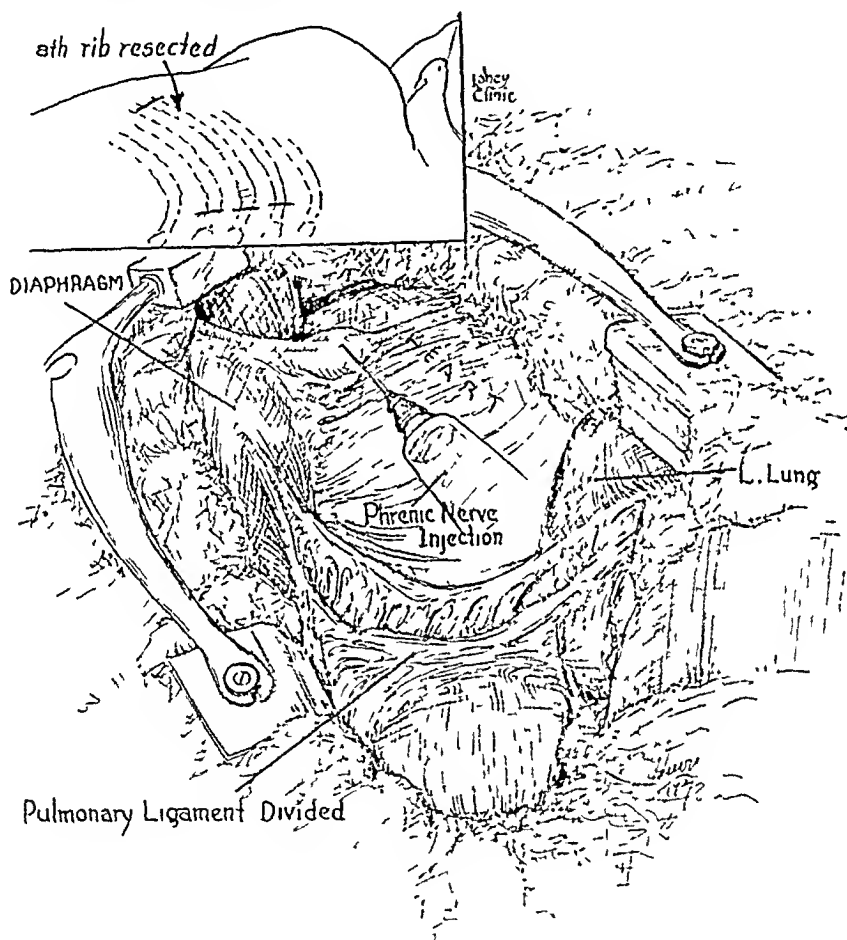


Fig. 7. Carcinoma of esophagus, lower third. Operation, transthoracic resection. Left thoracic cavity is opened through an infrascapular incision. Insert, eighth rib is resected and the seventh and ninth ribs are divided posteriorly. The inferior pulmonary ligament is divided and the left lung retracted, exposing diaphragm and mediastinum. The left phrenic nerve is infiltrated with novocain solution, 2 per cent.

has been established, have been reported in the literature. We have recently reported an example of successful resection with reestablishment of normal swallowing (3). Since this report, we have performed an exploratory operation in two other cases but were unable to resect the malignant tumor because of metastasis to the pleura in one case and in another because of extension to retroperitoneal glands. Resection has been carried out in three other patients, with one death after operation. The operation is performed through a left, infrascapular transpleural in-

implanted into the anterior wall of the stomach (Figs. 8 and 9). The rent in the diaphragm is then closed snugly about the stomach to prevent any herniation of abdominal viscera, thus making the stomach partly intrathoracic. The surgical management of these cases involves a considerable technical procedure but can be performed with a reasonable expectancy of success.

CASE REPORT

A man, aged forty-six years, came to the clinic July 29, 1937, because of pain in the epigastrium noted when swallowing food. The symptoms were of nine months'

duration and he had gradually limited his food to liquids and soft foods.

Other than evidence of loss of weight, the patient's general condition was good. Roentgenologic examination had revealed an obstruction at the lower end of the esophagus and microscopic examination of a specimen obtained from the tumor through an esophagoscope showed it to be an adenocarcinoma.

Operation was performed July 31, 1937, at which time, with the patient in the left lateral position, a long infrascapular incision was made on the left side parallel to the ninth rib, the trapezius was divided, the scapula elevated and the ribs exposed. The entire length of the ninth rib was removed, the eighth and tenth ribs were divided near the proximal ends and the pleura opened. The in-

Following operation convalescence was stormy but the patient finally recovered, and was discharged to his home, able to swallow quite normally. Fifteen months later after a fairly comfortable existence he died following recurrence of the tumor.

It is apparent that the patients to be submitted to such an extensive operation should be selected with great care. The collaboration of the internist, roentgenologist and surgeon is absolutely necessary. Obviously, any evidence of metastasis contraindicates surgical interference designed to remove the tumor. Evidence of a high degree of obstruction will in most cases indicate wide extension of the tumor and will

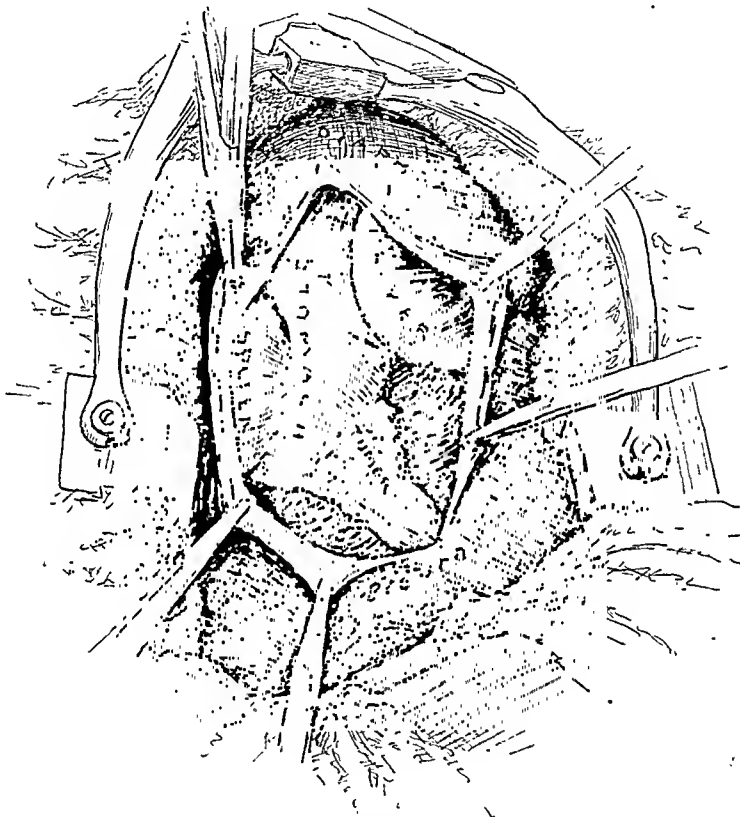


Fig. 8. Carcinoma of esophagus, lower third. The parietal pleura is incised exposing the esophagus and tumor. Diaphragm is opened radially in line of its muscle fibers showing the relationship of esophageal tumor to stomach and to liver and spleen.

ferior pulmonary ligament was divided and the lung retracted. The left phrenic nerve was injected with novocain and the esophagus exposed by incising the pleura over it. The diaphragm was then opened. The stomach was mobilized along its borders by dividing its attachments. The segment of esophagus containing the tumor was removed with the upper portion of the stomach, allowing a wide margin on either side of the tumor. The open end of the stomach was then closed by over and over catgut stitches and inversion completed with interrupted black silk stitches. The stump of the esophagus was then transplanted into the anterior wall of the stomach. The rent in the diaphragm was closed about the stump, thus making the stomach partly intrathoracic to bridge the gap caused by removal of the esophagus and part of the stomach, thus restoring gastro-esophageal continuity.

usually indicate an irremovable malignant tumor. Metastatic extension will involve not only local glands but very early will extend to glands along the lesser curvature of the stomach and to the retroperitoneal glands posterior to the lesser omental cavity. All patients should be examined under the fluoroscope and esophagoscopy should be performed to obtain a section of the tumor for microscopic examination before operation is advised.

The number of patients who have carcinoma of the lower third of the esophagus and upon whom such a procedure can be carried out is naturally limited, yet this operation offers a method of handling such patients who otherwise would go on to early death

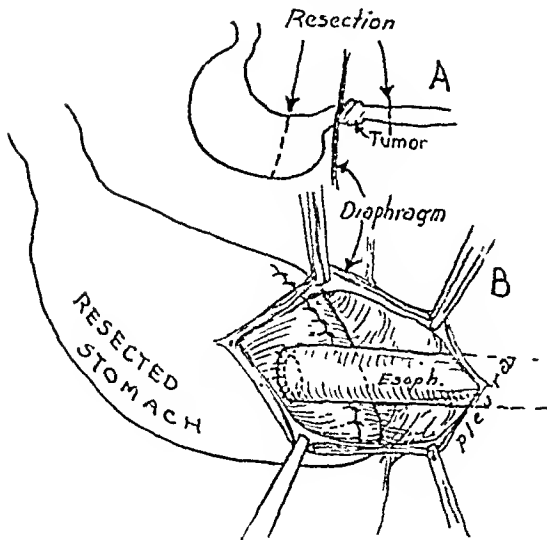


Fig. 9. Carcinoma of esophagus, lower third. *a*, Illustrating portion of stomach and esophagus containing tumor to be resected. The divided end of the stomach has been inverted. The esophageal stump has been transplanted into the anterior wall of the stomach, reestablishing continuity of esophagus with stomach. The stomach is brought partly into the thoracic cavity to bridge the gap caused by removal of a portion of the esophagus. The rent in the diaphragm is closed about the stomach.

unless an effort were made to remove the malignant tumor. One patient lived fifteen months, was able to swallow normally and was quite comfortable until the tumor recurred. In the other cases the operation was done too recently to be worth considering from the standpoint of prolongation of life or otherwise, yet in each case normal swallowing was possible.

This procedure can also be employed in patients in whom the malignant lesion arises in the cardia of the stomach and extends into the esophagus. One of our patients presented such a problem. The technical procedure is no more difficult because of this origin. This simply means that a somewhat greater segment of stomach must be taken. The stomach can be mobilized satisfactorily through the rent in the diaphragm and can be brought into the thoracic cavity to establish the esophageal gastric anastomosis.

Another problem of interest to the gastro-enterologist and somewhat less so to the surgeon is the matter of treatment of diverticula of the duodenum. Duodenal diverticula are not uncommonly demonstrated by roentgenologic examination of the duodenum, carried out in routine studies of the gastro-intestinal tract. They occur most frequently in the second part of the duodenum, near the ampulla of Vater or duct of Santorini, and commonly are noted upon the concave border of the duodenum. The next most frequent location is in the third part of the duodenum. They rarely are noted in the first part unless they appear as simple outpouchings of the duodenal wall, associated with duodenal ulcer.

Gastro-intestinal symptoms resulting from the presence of duodenal diverticula are not characteristic of the lesion and probably most diverticula do not give rise to symptoms. Gastro-intestinal distress arising in

the presence of a demonstrable duodenal diverticulum are those probably of an associated pathologic process resulting from disease of the gall bladder, ulcer or pancreatitis. Consequently, very few diverticula, duodenal in origin, will require operation to alleviate distress.

Inflammation arising in such diverticula, associated with delay in emptying the sac or due to irritation of contents of the sac or pressure of the filled sac upon the surrounding viscera, probably accounts for the symptoms noted. This distress commonly comes on a half hour or more after meals and may be confused with ulcer pain. The most common complaint is epigastric pain or heaviness, and nausea which may be associated with vomiting. Since the symptoms are not characteristic, the diagnosis must be made from roentgenologic findings. The treatment after ruling out all other causes for the abdominal discomfort, is medical, principally the employment of a nonirritating bland diet and various alkaline powders.

Very few patients with diverticula of the duodenum will need to be subjected to operation. Those on whom operation is carried out usually have large diverticula to which apparently the distress can be traced directly and which are thought to be chiefly responsible for the patient's symptoms.

Any operation upon a duodenal diverticulum may involve considerable risk because of the difficulty in exposing such a sac, which usually arises from the



Fig. 10. Diverticulum of duodenum. Roentgenogram shows duodenal cap well filled, smooth and symmetrical. The second part of the duodenum is narrowed, while posterior to and above the duodenum there is a large mass of barium which occupies a large diverticulum of the duodenum. The dotted line outlines the diverticulum.

second part of the duodenum and frequently is retroperitoneal in origin. One should, therefore, demonstrate in so far as possible that the symptoms arise from a diverticulum, that relief cannot be obtained from conservative medical measures, and before operation is advised one must be convinced from the location of the diverticulum that the lesion is in all probability safely removable. An illustration of such

a case in which operation was carried out is given below.

CASE REPORT

A woman, aged sixty-eight years, came to the clinic November 9, 1938. She had had epigastric distress of three weeks' duration. Pain was severe, occurred four hours after meals and was not relieved by soda or food. The pain was accompanied by slight flatulence but no nausea or vomiting. No weight loss was noted. Roentgenologic

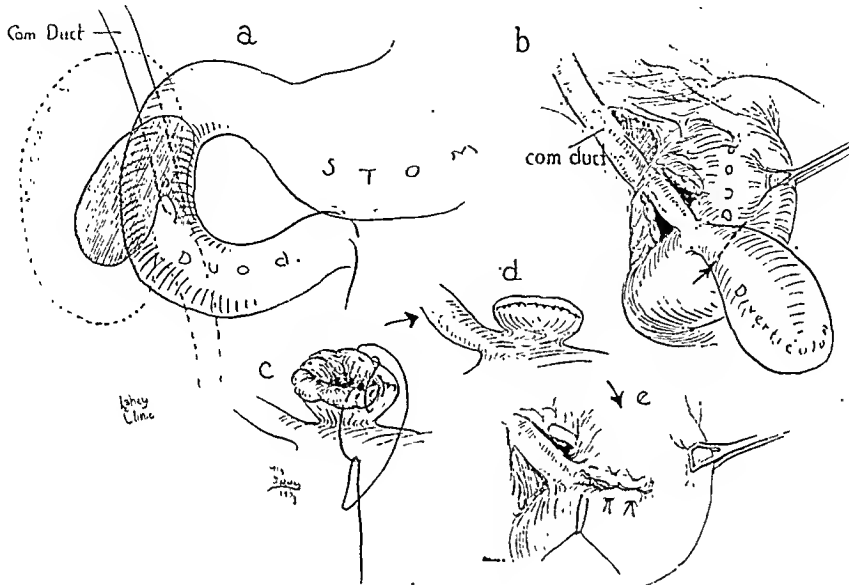


Fig. 11. Diverticulum of duodenum. Operation for removal. *a*, The relationship of diverticulum to duodenum, common bile duct and kidney is shown. *b*, The duodenum has been mobilized, the common bile duct and head of pancreas exposed. The diverticulum has been freed from surrounding structures. *c* and *d*, The diverticulum has been removed. The neck of the sac is closed by inverting sutures of catgut, reinforced with mattress sutures of silk.

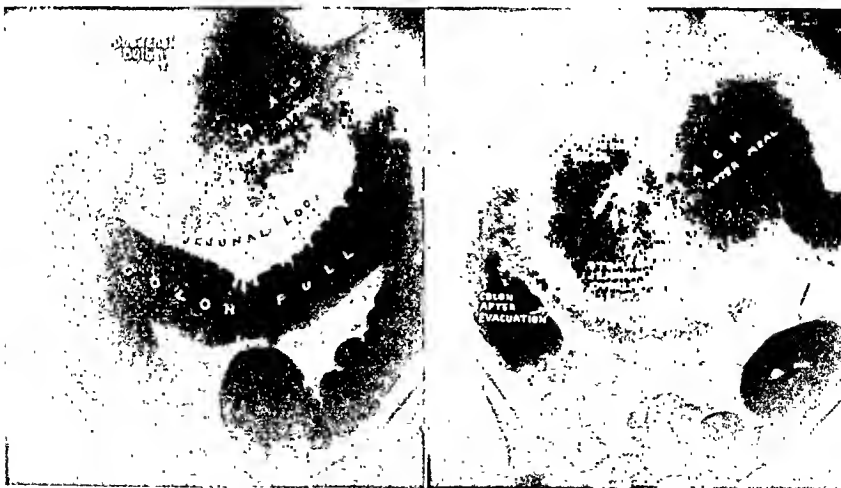


Fig. 12. Roentgenogram showing an obstructing lesion at the duodenojejunal junction as demonstrated by retained barium in a dilated stomach twenty-four hours following a barium meal. The duodenal cap, second and third portions of the duodenum are dilated three or four times their normal size. During the twenty-four hour period only a small amount of barium was seen to pass from the stomach into the dilated duodenum.

examination revealed that the duodenal cap filled well, was smooth and symmetrical. The second part of the duodenum was somewhat narrowed, while posterior to and above the duodenum there was a large mass of barium which had the appearance of a loop of intestine, but was located in the position of the gall bladder (Fig. 10). Cholecystograms were normal.

At operation, a very large diverticulum, 3 inches in diameter, was found arising from the posterior wall of the duodenum near the ampulla of Vater. The diverticulum lay posterior and lateral to the duodenum and was retroperitoneal. The sac was dissected free from the surrounding structures and was found attached to the posterior wall of the duodenum by a narrow neck. The diverticulum was removed, the neck of the sac ligated and inverted into the duodenal lumen, reinforcing the duodenal wall in this region with silk sutures (Fig. 11). Following operation the patient's course was afebrile, food

was taken without distress, and she was discharged from the hospital eighteen days after operation.

Tumors of the small bowel are of relatively infrequent occurrences and rarely present any great technical difficulty in their surgical removal, provided, of course, metastasis and extension permit resection. Kiefer (4) reported thirteen cases of tumor of the small bowel from The Lahey Clinic (1933) and in a later report Chamberlin (5) (1938) added nine cases. Of the total group of twenty-two cases, ten involved the jejunum. Malignant tumors of the jejunum may originate high in the jejunum or even at or just beyond the ligament of Treitz. Such a high origin of a malignant tumor in the jejunum may present a considerable problem in the surgical management because following resection of the segment containing the tumor, the remaining jejunal stump may be too short to make a satisfactory end-to-end anastomosis. When the tumor has been found to involve the jejunum at the ligament of Treitz the tendency has been to perform a transmesocolic anastomosis of the duodenum and jejunum and to make no attempt at removal of the malignant lesion. In spite of the level of origin of these tumors many prove resectable and the problem becomes a technical one, that of reestablishing a safe intestinal continuity. The case report given below illustrates a method devised and employed by one of us in handling successfully such a situation.

CASE REPORT

A woman, aged fifty-eight years, was seen in the clinic October 12, 1938, because of severe epigastric distress of six weeks' duration and vomiting for the last five days. Physical examination did not reveal tenderness, spasm or masses in the abdomen. Erythrocytes numbered 4,960,000 and leukocytes 5,000. On gastric analysis, the total acid was 20 and the free acid 7. Roentgenologic examination revealed an obstructing lesion at the junction of the duodenum and jejunum, without definite characteristics (Fig. 12). A diagnosis was made of jejunal obstruction probably due to carcinoma, and operation was advised.

October 17, a loop of jejunum 18 inches in length was resected and a side-to-side antecolic duodenojejunosomy was performed. The pathologist's report was adenocarcinoma; two lymph nodes which were removed with the specimen were reported to be normal. After removal of the segment of the jejunum containing the tumor (Fig. 13), the remaining intraperitoneal jejunal loop was too short to make a satisfactory and safe end-to-end anastomosis possible. The upper and lower ends of the remaining jejunum were closed by inversion with catgut, and reinforced with mattress sutures of black silk. The right hepatic flexure of the colon was then entirely mobilized and the transverse colon freed up to its middle portion (Fig. 14). The hepatic flexure was turned toward the midline and the retroperitoneal duodenum exposed and mobilized throughout its entire extent. An incision was then made in the ligament of Treitz, freeing the upper stump of jejunum which was reduced toward the right side beneath the root of the mesenteric vessel. The jejunal stump was thus entirely freed with its mesentery intact, brought over in front of the transverse colon and a lateral anastomosis readily made with the lower stump of the jejunum (Fig. 15). Following operation, recovery was uneventful, with no obstruction at any time and with complete and immediate establishment of the fecal stream.

SUMMARY

Some complicated gastro-enterologic problems with which we have had to deal are discussed and the plans which we have employed in their management are

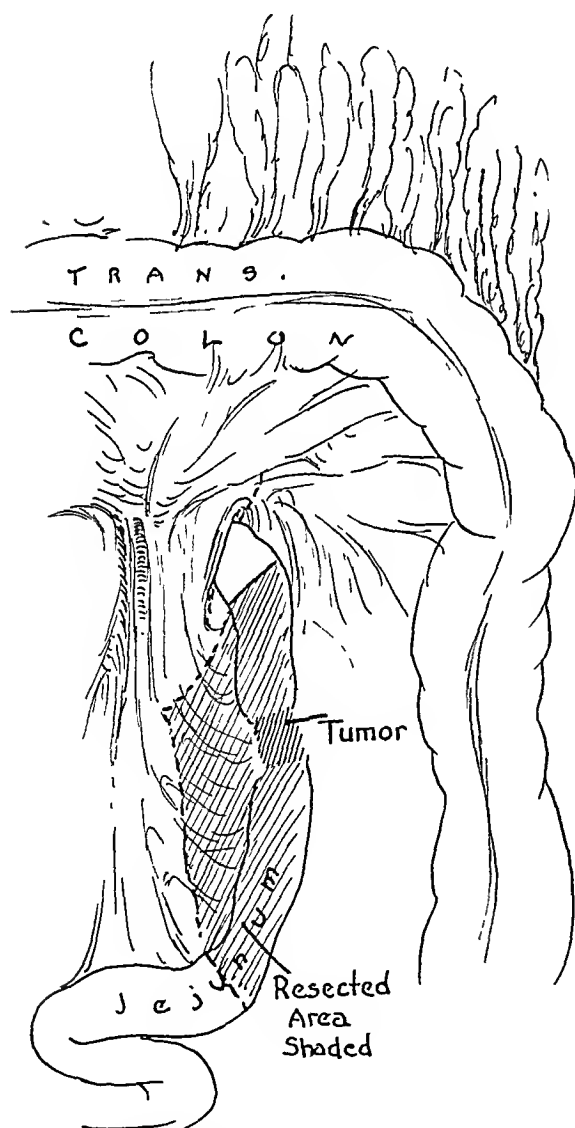


Fig. 13. Carcinoma of the jejunum. Drawing shows segment of jejunum with tumor. The relationship to the colon and Treitz ligament is illustrated.

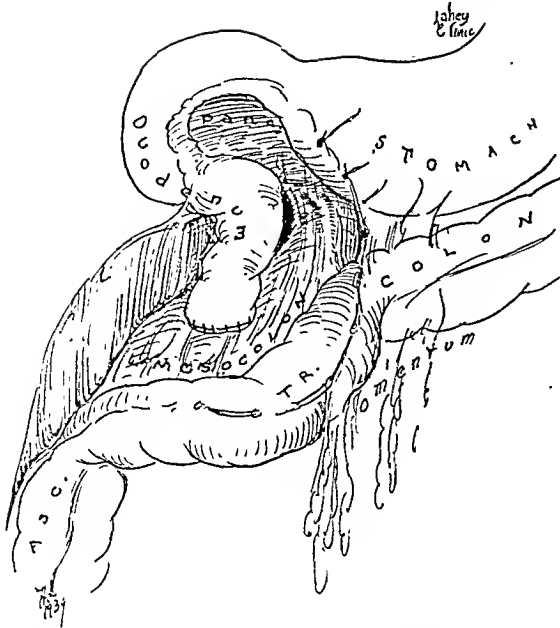


Fig. 14. Carcinoma of the jejunum. The hepatic flexure of the colon has been mobilized and the transverse colon also mobilized to its mid portion. The proximal end of the jejunum following resection of the tumor has been reduced beneath the root of the mesenteric vessel. The jejunal stump is thus freed with its mesentery intact and brought anterior to the transverse colon.

presented. These include a two stage plan which we have employed in the management of a large gastro-jejunal fistula; total gastrectomy for gastric carcinoma; experiences with transpleural resection of the lower end of the esophagus for malignancy with restoration of swallowing; the management of duodenal diverticula, and a plan for successfully restoring the fecal stream in high jejunal resection with a short jejunal stump.

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DISCUSSION

DR. SAMUEL F. MARSHALL (Boston): Mr. President and Members of the Association: Certainly an aggressive attitude in the surgical management of these cases is justifiable, but only if we can show a lowered morbidity and mortality. If an increased number of months or years of the patient's life can be obtained and relief of some of the disturbing symptoms results, certainly I think the surgical procedure is justifiable.

It has been proven quite conclusively that total gastrectomy can be done with a lowered mortality and with practically no morbidity following the operation. As Dr. Lahey has told you, we have done total gastrectomy in twenty cases with five deaths. In the last eleven cases two deaths occurred. One was in one of my cases in which I am sure that the operation was poorly chosen.

Several factors influence the lowered mortality and morbidity. Perhaps the outstanding and the most influential factor is the employment of nupercaine in spinal anesthesia. I am sure this has reduced the morbidity and lowered the mortality because this anesthesia produces better conditions for operation and pulmonary complications can be avoided.

An important factor which is always present and of which we are always aware is the experience of the surgeon.

Another factor I would emphasize is the employment of nonabsorbable sutures in carrying out extensive resections such as total gastrectomy.

Total gastrectomy can be done readily, particularly with the type of anesthesia we employ now. It is a painstaking procedure, but not a very difficult procedure. We do not think it necessary to divide the costal margin to get exposure.

The other problem that interests me, and which Dr. Lahey has presented to you, is resection of carcinoma of the lower third of the esophagus. As Dr. Lahey said, we are not prideful of the report of these cases, but we feel rather that they represent an advance. This procedure is not original but we hope at least to do something for these patients if we can get them early enough. They should be referred early enough to permit such a radical procedure to be carried out and the problem of early recognition belongs to the general practitioner.

I know that you are aware that carcinoma of the lower third of the esophagus metastasizes early and may involve the glands along the lesser curvature of the stomach. There is no possible way of telling the extent of metastasis until operation is performed.

Exploratory operation should be carried out trans-thoracically. It is a simple procedure. One rib can be removed, the lung retracted and the surgeon can determine if the case is operable.

We have had four cases in which carcinoma of the esophagus was removed. One death occurred which probably was due to the fact that the phrenic nerve was not permanently disabled.

This operation makes it possible to remove lesions of the esophagus if they are recognized early.

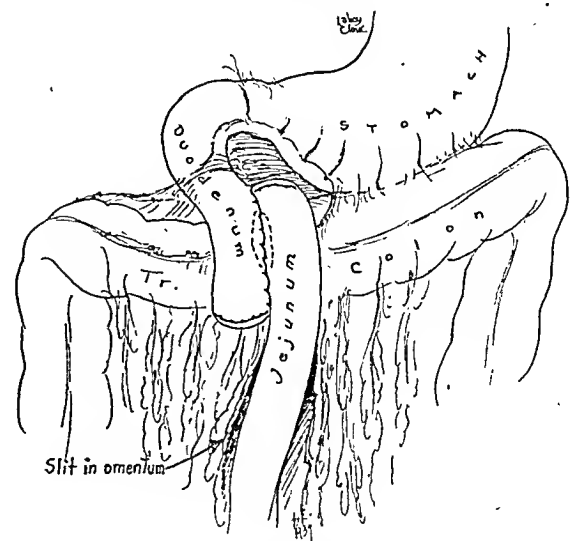


Fig. 15. Carcinoma of the jejunum. The omentum is divided vertical to its attachment to the transverse colon. The mobilized proximal jejunal stump is brought in front of the transverse colon and a lateral anastomosis is made with the lower stump of jejunum, thus restoring intestinal continuity.

Abstracts

BIBLIOGRAPHY ON NORMAL NUTRITION

Arranged by The American Dietetic Association, Community Education Section, 1938-39.

The purpose of this compilation is to meet the needs of members of the medical and dental professions, students and internes, who wish to know of books on nutrition so that they may keep abreast in this rapidly developing field. Some books have been included, of a more "readable" type, which may be recommended to the intelligent layman.

REFERENCE AND TEXT BOOKS ON NUTRITION

1. A Series of Articles on the Present Status of Our Knowledge of the Vitamins. Price \$2.50, pp. 580. Chicago: American Medical Association, 535 N. Dearborn St., 1939.

The articles in this series were prepared under the auspices of the Council on Pharmacy and Chemistry and the Council on Foods.

2. Nutrition and Public Health by Et. Burnet and W. R. Aykroyd (reprint No. 2 from Quarterly Bulletin of the Health Organization, League of Nations) June, 1935. Price \$0.50, pp. 152. New York: Columbia Univ. Press.

This report is addressed primarily to public health authorities. The data selected show the remarkable world-wide advances of the science of nutrition and its present problems. After introductory chapters on the problems which confront dietitians today and the fixing of dietary standards, the editors consider the world's food supply, its production, distribution and preservation, the influence of poverty and unemployment on diet, infant and child nutrition, the food deficiency diseases and have added an interesting study on collective feeding.

3. Nutrition of the Infant and Child. By Julian D. Boyd, B.S., M.S., M.D., Asso. Prof. of Pediatrics, State University of Iowa. Edited by Morris Fishbein, M.D. Price \$3.00, pp. 198, with 40 illustrations. New York: National Medical Book Co., Inc., 1937.

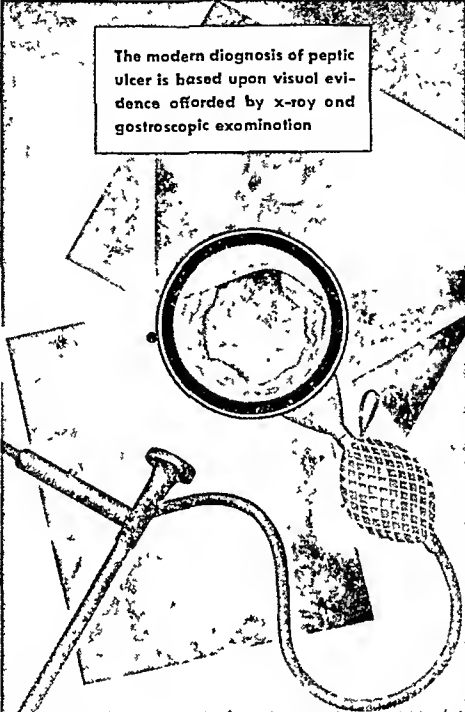
This monograph is a summary of nutrition in pediatrics. It is written from a critical viewpoint. The contents are divided into sections on the principles of nutrition, foods for the normal infant and child, and nutrition during illness. In a few pages at the end, practical diet lists and schedules are provided for normal infant feeding and for therapeutic dietetics.

4. Nutrition. By Margaret S. Chaney, Ph.D. Prof. of Home Economics, Connec. College, and Margaret Ahlborn, M.S., Prof. of Nutrition, Kansas State College. Price


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\$3.00, pp. 436. Boston: Houghton Mifflin Co., 1939.

A text book for college students in nutrition.

5. Nutrition in Health and Disease. By Lenna F. Cooper, Edith M. Barber and Helen S. Mitchell, Ph.D. Price \$3.00, pp. 708. Philadelphia: J. B. Lippincott Co., 1938.

A text and reference for physicians, students of nutrition and dietitians who teach nurses. The book is in seven parts, (1) normal nutrition, (2) diet in disease, (3) feeding of mother and child, (4) nutrition and the public health program, (5 and 6) food selection and cookery for normal

and for sick and convalescent and (7) an appendix.

6. The Avitaminoses. By Walter H. Eddy, Ph.D. and Gilbert Dalldorf, M.D. Price \$4.50, pp. 338. Baltimore: The Williams and Wilkins Company, 1937.

This book is the result of eight years of collaboration between Professor Eddy, a biochemist engaged in nutrition research and Dr. Dalldorf, a physician and pathologist. The purpose of the book is to call attention to pathological responses—sub-clinical and acute—to vitamin deficiencies in the diets of human beings as well as of experimental animals.

7. Vitamins in Theory and Prac-

tice. By Leslie J. Harris, Sc.D., D.Sc., Nutrition laboratory, Univ. of Cambridge and Medical Research Council. Price \$4.00, pp. 240. New York: The Macmillan Co., 1937.

Dr. Harris explains in entertaining and simple fashion how the various vitamins were discovered, and how they work in the human system.

8. Vitamins and Vitamin Deficiencies. I. Introduction and Historical, Vitamin B₁ and Beri-beri. By Leslie J. Harris. Vol. 1, pp. 218. London: J. and A. Churchill, 1938.

This volume, which has a foreword by F. G. Hopkins, is the first of a series planned to provide a comprehensive synopsis of the results of modern research on each of the known vitamins.

9. Biochemistry for Medical, Dental and College Students. By Benjamin Harrow, College of City of New York. Price \$3.75, pp. 385. Philadelphia: W. B. Saunders Co., 1938.

The latest developments in the field of animal biochemistry are contained in this text book. One of the 24 chapters is devoted to a discussion of the biochemical aspects of the nervous system and another to the hormones in connection with the glands which manufacture them. The appendix contains tabular data on the nutritive value of foods.

10. The Newer Knowledge of Nutrition. By E. V. McCollum, Ph.D., Sc.D., Prof. of Biochemistry; Elsa Orent-Keilcs, Sc.D., Associate in Biochemistry; and Harry G. Dav, Sc.D., Associate in Biochemistry; School of Hygiene and Public Health, Johns Hopkins University. Fifth edition. New York: The Macmillan Co., 1939.

A standard reference book for physicians, dietitians and students. The chapters on dietary habits of man in different parts of the world and on deficiency diseases are of particular interest to public health workers.

11. The Foundations of Nutrition. By Mary Swartz Rose, Ph.D., Prof. of Nutrition, Teachers College, Columbia University. Third edition. Price \$3.50, pp. 625. New York: Macmillan Co., 1938.

This text on nutrition is "a gold mine of information . . . one of the best and simplest expositions in the English language."

12. Vitamin B₁ (Thiamin) and Its Use in Medicine. By Robert R. Williams, Sc.D., Bell Telephone Laboratories, and Tom D. Spies, M.D., associate professor of medicine, Univ. of Cincinnati. Price \$5.00, pp. 411. New York: The Macmillan Co., 1938.

Dr. Williams probably has done more than any other person in investigating the properties of Vitamin B₁ and was awarded the Willard Gibbs Medal of the American Chemical Society. Methods of application of these research findings to actual

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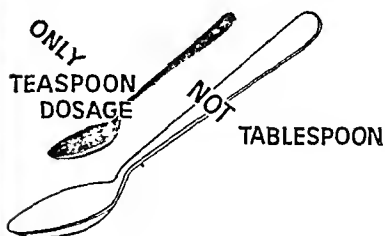
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Those are the words of Dr. William DeKleine, Medical Director of the American Red Cross. Since 1927, when the Mississippi Valley flood brought to light the extent of the ravages of pellagra in the south, the Red Cross has been waging continuous battle against this death dealing invader. Pure yeast and garden seed have been the ammunition, fortified with a verbal barrage to impress the country of the seriousness of this disease and the comparative ease with which it may be eradicated.

During the eight years from 1927 to 1935 the Red Cross through its chapters distributed more than 500,000 pounds of pure yeast, and 750,000 packages of garden seeds. Each package was large enough to plant between a quarter and half an acre of garden.

The most important result of this activity has been a drop in the annual pellagra death rate from 7,000 to 3,000 or less. Other incidental results have also been achieved. Thousands of acres were converted into gardens where gardening had become a lost art; canning again became popular and provided protection during winter months. Health departments, physicians and others helped in this drive to free the section of the scourge.

Pure yeast is one of the most potent remedies known for the treatment of pellagra. In proper dosage it will usually cure in six to ten weeks — even without alteration of the usual harmful diet of pork, molasses and meal.

So says Dr. DeKleine, and he should know. The Red Cross continues instruction in nutrition through its many hundred chapters, and continues to promote gardening and the distribution of yeast. To continue and expand work of this kind, the Red Cross is seeking 1,000,000 new members during its annual Roll Call, from Armistice Day to Thanksgiving this year. Membership dues finance all day-to-day work of the Red Cross, and only in time of great disaster are special contributions and gifts called for.

clinical practice make the book invaluable alike to the physician, the biologist and the student of nutrition.

MORE READABLE—LESS TECHNICALLY WRITTEN BOOKS

1. The Normal Diet. Council on Foods, American Medical Association. Free, pp. 16. Chicago: American Medical Association, 1938.

2. Your Diet and Your Health. By Morris Fishbein, M.D., Editor, Journal of the American Medical Association. Price \$2.50, pp. 298. New York: McGraw Hill Book Co., 1937.

In a simple language, interestingly

written, are given the most generally recognized and accepted truths about diet.

3. Man, Bread and Destiny. By C. C. Furnas, Asso. Prof. of Chemical Engineering, Yale University, and S. M. Furnas, formerly instructor in Nutrition, Univ. of Minnesota. Price \$5.00, pp. 364. Baltimore: Williams & Wilkins Co., 1937.

"In the light of the knowledge which we now have on the influence of food on physical and mental fitness, the authors review the course of civilization and show how changes in

food supply have been responsible for the waxing and waning of races and nations. This book does not bring to light any facts new to those who have thoroughly studied the subject; it is a book for the intelligent layman rather than the student. The authors write from a wide knowledge and with a sense of humor which makes the book easy and interesting to read." J. B. Orr.

4. Have You Had Your Vitamins? By Harry N. Holmes, Ph.D. Severance Chemical Lab., Oberlin College. Price \$1.00, pp. 60. New York: Farrer & Rinchart, 1938.

"It is significant that Dr. Holmes, a leader in pure science, who has himself recently made the significant contribution of securing Vitamin A in crystalline condition, has in this little volume endeavored to summarize and briefly interpret for the layman the practical aspects of our vitamin knowledge. An excellent balance has been maintained between the interesting historical developments, our present knowledge, and the practical aspects of vitamin administration." Ind. and Eng. Chem.

5. Food, Nutrition and Health. By E. V. McCollum, Ph.D., Prof. of Biochemistry, and J. Ernestine Becker, M.A. (title) School of Hygiene and Public Health, Johns Hopkins Univ., 4th edition, revised. Price \$1.50, pp. 154. Baltimore: Published by the authors, 1937.

A guide for the application of the science of nutrition to the health of the individual. The subject matter is presented in non-technical style, understandable to the intelligent reader.

6. Faets, Fads and Frauds in Nutrition. By Helen S. Mitchell, Ph.D. and Gladys M. Cook, Mass. State College. Price, free, pp. 32. Amherst, Mass.: Mass. Agric. Expt. Station.

This bulletin has been written for a nutrition-conscious public which has a limited basis for evaluating the merits of claims made in advertising and by the proponents of fads.

7. The Deuce of Reducing. By Katherine Mitchell, Dietitian, Los Angeles County General Hospital. Price \$1.50, pp. 112. New York: Covici Friede, Publishers, 1937.

This book will be read easily because of its witty style, agile and spicy, but keyed to the times. A helpful introduction by Dr. Morris Fishbein supplements Miss Mitchell's warning of the dangers of radical reducing without medical supervision.

8. The Normal Diet and Healthful Living. By W. D. Sansum, M.D., Chief of Staff of Sansum Clinic and Director of Metabolic Research Dept., Cottage Hospital, Santa Barbara, Calif.: R. A. Hare, M.D., Sansum Clinic and Ruth Bowden, B.S., Dietitian Sansum Clinic. Price \$2.00, pp.



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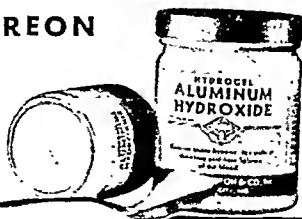
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245. New York: The Macmillan Co., 1938.

A concise summary of the type of instructions the authors have been giving their patients for a number of years and which they say "has resulted in good both to patients and authors."

9. Vitamin Chart. Nutrition Service, Division of Maternity, Infancy and Child Hygiene, New York State Department of Health, Albany, N. Y. Single copies are free. 1 sheet 8½" x 11".

10. The A B C of the Vitamins: A Survey in Charts. By Jennie Gregory. Price \$3.00, pp. 93. Baltimore: The Williams and Wilkins Company, 1938.

The story of the vitamins presented by means of charts and graphs in a 9 x 12 inch volume.

RECENTLY PUBLISHED REVIEW ARTICLES

1. Nutrition and the Health of the School Child. Mary Swartz Rose, Ph.D., Teachers College, Columbia Univ., Jour. Amer. Dietetic Asso., 15, 63, Feb., 1939.

2. Present Status of Dental Caries in Relation to Nutrition. Nina Simmonds, Sc.D., Univ. of California College of Dentistry. Amer. Jour. Public Health, 28, 1381, Dec., 1938.

3. The Relation of Nutrition to the Development of Sound Teeth. E. N. Todhunter, Ph.D., Asso. Prof. of

Nutrition, State College of Washington. Jour. of Home Econ., 30, 93, Feb., 1938.

4. The More Abundant Diet. James S. McLester, M.D., The Univ. of Alabama. Jour. Amer. Dietetic Asso., 14, 1, Jan., 1938.

5. Recent Advances in Nutritional Research. E. V. McCollum, Ph.D. Johns Hopkins Univ. Jour. Amer. Dietetic Asso., 14, 8, Jan., 1938.

6. Nutritional Deficiency. George E. Minot, M.D., Harvard Univ. Med. School. Annals of Internal Medicine, 12, 429, Oct., 1938.

7. Diseases of Metabolism and Nutrition. Review of Recent Contributions. Dwight L. Wilbur, M.D., Univ. of Calif. Published each year in March issue Archives of Internal Medicine.

SHORT-WAVE ULTRA-VIOLET RADIATION

Germ-killing radiation from short-wave ultra-violet tubes is the dairy industry's latest answer to the problem of sanitary control of milk-bottling and distribution.

Constituting the first practical large-scale application to inorganic materials of General Electric's recently-introduced germicidal lamps, the new sanitary control method was demonstrated here this afternoon to state health officials and dairy industry leaders by R. J. Alden, Sanitation Engineer of the Cowdrey Products Company, manufacturers of milk bottle hood-caps and machinery for the dairy industry.

Employing twenty-one of the new germicidal lamps, the installation continuously irradiates the hood-caps from the moment the paper is unrolled until the finish of the manufacturing process, when the hood-caps are inserted into sealed containers.

Rigid tests of the new method, conducted during the last three months under the supervision of John B. Enright, milk Bacteriologist of the City of Fitchburg, show that it reduces the bacteria-colony count on the hood-caps applied to the pouring-lips of milk bottles—a major focal point of infection—from the commonly accepted limit of 500 bacteria-colonies to an average of less than ten.

It was revealed by Mr. Alden that the new germicidal irradiation process was recently described to Lester T. Tompkins, Director of the Division of Dairying and Secretary of the Milk Regulation Board of the Commonwealth of Massachusetts, in the presence of Governor Leverett Saltonstall and William Casey, State Commissioner of Agriculture, who has jurisdiction over all regulations pertaining to the production and distribution of milk. In a releasable written communication to the Cowdrey company, following the meeting, Mr.

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1. Copeman, W.S.C.: The Medical Standard, "Some Principles in the Modern Treatment of Rheumatic Diseases," p. 12, May, 1930. 2. Illinois Medical Journal, September, 1930, p. 2231. 3. New and Non-Official Remedies, pub. by Amer. Med. Assoc., p. 370, 1934.

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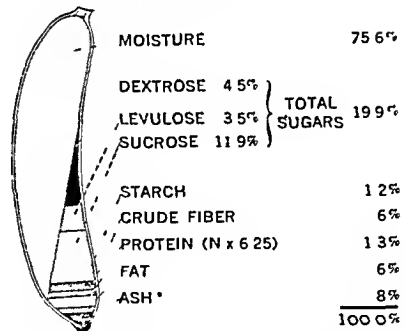
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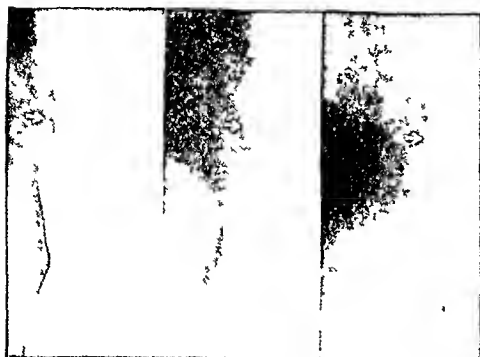
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Corn Meal	100 g	360	3.0	1000	100 g	360	3.0	1000	
Wheat Meal	100 g	340	2.8	800	100 g	340	2.8	800	
Barley Meal	100 g	320	2.6	700	100 g	320	2.6	700	
Oat Meal	100 g	300	2.4	600	100 g	300	2.4	600	
Rice	100 g	280	2.2	500	100 g	280	2.2	500	
Peas	100 g	260	2.0	400	100 g	260	2.0	400	
Spinach	100 g	240	1.8	300	100 g	240	1.8	300	
Tomatoes	100 g	220	1.6	200	100 g	220	1.6	200	
Apples	100 g	200	1.4	100	100 g	200	1.4	100	
Oranges	100 g	180	1.2	100	100 g	180	1.2	100	
Bananas	100 g	160	1.0	100	100 g	160	1.0	100	
Grapes	100 g	140	0.8	100	100 g	140	0.8	100	
Strawberries	100 g	120	0.6	100	100 g	120	0.6	100	
Raspberries	100 g	100	0.4	100	100 g	100	0.4	100	
Blueberries	100 g	80	0.2	100	100 g	80	0.2	100	
Blackberries	100 g	60	0.1	100	100 g	60	0.1	100	
Cherries	100 g	40	0.1	100	100 g	40	0.1	100	
Peaches	100 g	20	0.1	100	100 g	20	0.1	100	
Plums	100 g	10	0.1	100	100 g	10	0.1	100	
Applesauce	100 g	1	0.1	100	100 g	1	0.1	100	
Orange Juice	100 g	1	0.1	100	100 g	1	0.1	100	
Apple Juice	100 g	1	0.1	100	100 g	1	0.1	100	
Peasauce	100 g	1	0.1	100	100 g	1	0.1	100	
Spinach Sauce	100 g	1	0.1	100	100 g	1	0.1	100	
Tomato Sauce	100 g	1	0.1	100	100 g	1	0.1	100	
Apple Sauce	100 g	1	0.1	100	100 g	1	0.1	100	
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Prompt Symptomatic Relief in PEPTIC ULCER

...with **PLAIN KNOX
GELATINE (U. S. P.)**



CASE I—FEMALE, 74

Uncomplicated gastric ulcer first demonstrated by Roentgen rays in 1934. Diet and alkalies afforded little relief. Accompanied by loss of weight. Repeated X-ray studies in 1936 and 1937 showed no improvement. She was placed on a diet-gelatine regime in November, 1937. Relief immediate. Gained weight. Roentgen studies in April, 1938 showed no demonstrable ulcer.

NOTE:

The gelatine used in this study was plain Knox Gelatine (U.S.P.) which assays 85% protein and which should not be confused either with inferior grades of gelatine or with sugar-laden dessert powders, for these latter products will not achieve the desired effects. When you desire pure U.S.P. Gelatine, be sure to specify KNOX. Your hospital can get it on order.

CLINICAL research has recently demonstrated the effectiveness of utilizing plain Knox Gelatine (U.S.P.) in treatment of peptic ulcer. In a group of 40 patients studied, 36 (or 90%) were symptomatically improved; 28 of these (or 70%) experienced *immediate relief of all symptoms*. Other than dietary regulation which included frequent feedings of plain Knox Gelatine no medication was given except an occasional cathartic.

NO DANGER OF ALKALOSIS

This regime thus eliminates the "alkalosis hazard" attendant upon continued alkali therapy. In discussing the mode of action by which gelatine brings peptic ulcer relief, Windwer and Matzner* speak of the acid-binding properties by which proteins can neutralize acids, and they state that the frequent gelatine feedings "apparently caused more prolonged neutralization of the gastric juice."

PEPTIC ULCER FORMULA

Empty one envelope Knox Gelatine in a glass three-quarters filled with cold water or milk. Let the liquid absorb the gelatine. Then stir briskly and drink immediately before it thickens. Take hourly between feedings for seven doses a day.

*Windwer and Matzner, *Am. Jl. Dig. Dis.* 5:743, 1939.

WRITE DEPT. 475

KNOX GELATINE LABORATORIES
JOHNSTOWN NEW YORK

Please send complete details of the Knox Gelatine peptic ulcer regime.

Name _____
Address _____
City _____ State _____



search at Princeton on Wednesday, September 6.

The program at New Brunswick will be divided into two sections, exhibitions and charts illustrating new developments in the Squibb Institute, and a display of biological products developed by large scale methods in the Biological Laboratories. German, Spanish, French and Italian interpreters will be provided for those who do not speak English. Stables in which 200 horses and 1500 rabbits are maintained for the production of antitoxic and antibacterial sera will be shown to the foreign microbiologists.

The new virus laboratory is housed in a specially constructed building,

and is equipped for work with chick embryos and tissue culture, two of the techniques for work in this field. The actual working quarters consist of a large general laboratory equipped with every facility for chemical and histological work, a general preparation room for washing, drying, packing and storing the various materials that are used, two special culture and operating rooms provided with filtered ventilation, a spacious incubator room, an animal preparation room, a bleeding room and ample animal quarters.

The arrangement of the rooms is such that the air of the culture suite proper is protected at all times from

the air of the general laboratory and office quarters on the one side, and of the animal room on the other. It is also possible for visitors to observe every step of the work in progress without entering any of the various rooms of the culture suite.

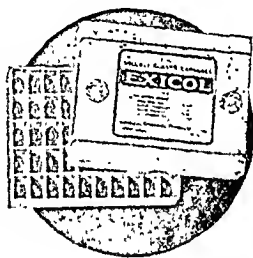
The program of the visiting scientists at New Brunswick includes a demonstration of the Institute's work on the effects of Vitamin K and some of the new simple synthetic products which have an effect similar to that of the natural vitamin. A test, using baby chicks and allowing Vitamin K to be assayed in six hours, will be carried out. Charts will show the relationship of Vitamin K deficiency to blood clotting, a comparison of methods of assay of Vitamin K, and the isolation of the natural vitamin from alfalfa. Natural and synthetic products with Vitamin K activity will be displayed.

Dr. Parker was born in Newport, Nova Scotia, on October 18, 1903. He received the degree of Bachelor of Arts from Acadia University in 1924, and the degree of Doctor of Philosophy in 1927 from Yale University, where he was Sterling Fellow, and assistant in zoology. From 1927 to 1929 he studied in Germany as National Research Council Fellow in biology. He became assistant in the division of experimental surgery at the Rockefeller Institute in 1930, and associate in 1935. His researches have dealt with selection in protozoa and the biology of tissue cells in pure cultures. Dr. Parker is the author of the leading text on "Methods of Tissue Culture."

WOLDMAN, EDWARD E. AND POLAN, CHARLES G.

Am. J. Med. Sci., Cleveland, Ohio, p. 155, Aug., 1939.

The continuous drip method of using colloidal aluminum hydroxide has been in use three years; it is especially designed to neutralize gastric acidity uninterruptedly and thereby allow peptic ulcer to heal. The purpose is the same as most of other forms of treatment for ulcer but as Crohn and Reiss have shown magnesium oxide and sodium bicarbonate are the most powerful excitants of gastric secretion, excepting histamine. Colloidal aluminum hydroxide is mildly astringent and non-irritating. It is amphoteric, with a pH of 6.9; and does not cause alkalosis. It contains about 5% of aluminum hydroxide and about 0.6% of sodium chloride in water. It combines with 12 times its volume of tenth-normal hydrochloric acid within half an hour. It is not absorbed from the gastrointestinal tract, as shown by Ivy, in dogs and by Einsel, Adams and Myers, in man. It coats the ulcer with a jelly-like mass. It is helpful in



EXICOL

(Oleic Acid and Bile Salts)

Merits Your Serious Consideration Because . . .

1. It is a potent and proven cholaretic and cholagogue—stimulating both bile secretion and gall bladder emptying.
2. The clinical results obtained with Exicol tend to prove the correctness of the physiologic principles upon which this theory is based.
3. It is a rational and dependable adjunct in the therapy of non-surgical diseases of the biliary tract.
4. Exicol therapy makes feeding of high fat diets unnecessary.

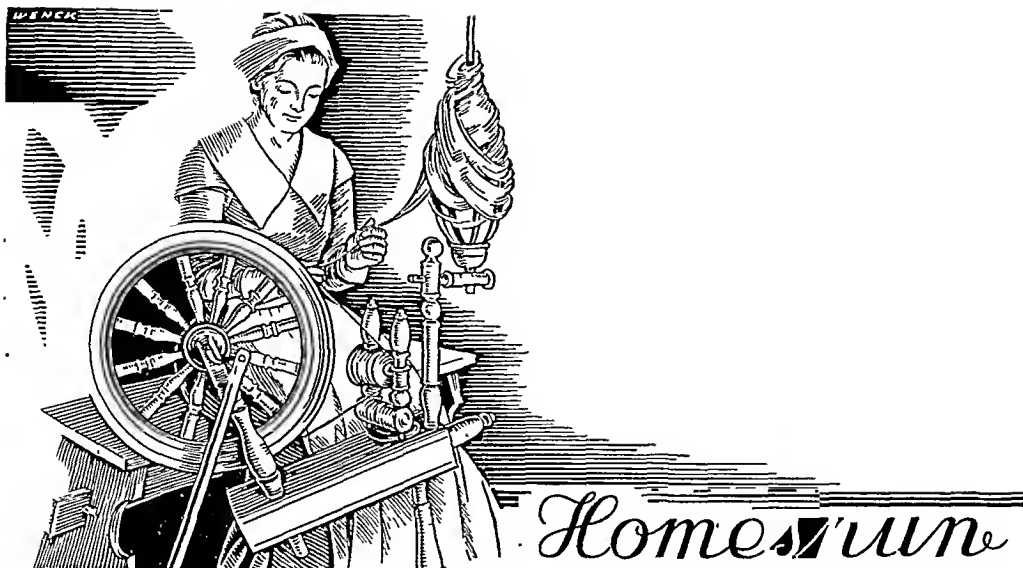
Exicol is indicated in the treatment of chronic cholecystitis, chronic cholangitis, toxic hepatitis and functional biliary insufficiency.

Dosage: Two capsules three times daily before meals.

Supplied in boxes of 36 and 100 capsules.

Literature on Request

Brooklyn Scientific Products Co. Inc.
70 Fifth Avenue New York, N. Y.



Cloth and Home-Brewed "Remedies"

Homespun cloth still has its quality appeal but home-brewed remedies are done with. Advanced methods in the art of pharmacy have replaced the rule-of-thumb of the kitchen chemist.

An impressive example of modern exacting compounding is Loraga, in which so fine an emulsification of mineral oil and agar is attained that thorough mixing with the intestinal contents is assured and leakage obviated. A pleasing taste is achieved without artificial flavoring. Absence of sugar, alcohol and alkali in Loraga makes it suitable for all age periods.

Loraga contains no added laxative ingredients. A fine mineral oil emulsion, indeed, in the treatment of the costiveness of children and adults when no active peristaltic stimulation is indicated. You can obtain a trial supply of Loraga by writing for it on your letterhead.

L O R A G A

A PLAIN MINERAL OIL EMULSION AT ITS BEST

A WILLIAM R. WARNER PRODUCT

SUPPLIED IN 16-OUNCE BOTTLES

WILLIAM R. WARNER & CO., INC., 113 West 18th Street, New York City

arresting hemorrhage. The drip must be continued throughout the night and not more than one hour should elapse without medication. In the healing of an ulcer the granulation is extremely friable and must be protected until the crater is filled in, which requires 7 to 10 days. The method has been used successfully in bleeding ulcers as it promotes clot formation and then protects the delicate fibrin from the action of the unbuffered gastric juice, and pepsin is not active in alkaline or neutral solutions.

The treatment requires hospitalization of the patient. The colloidal aluminum hydroxide diluted to 25% is instilled into the stomach through

a naso-gastric collapsible thin rubber tube, $\frac{1}{4}$ inch in diameter, passed with the aid of silkworm-gut suture which is left in place. The tube is passed only as far as the lower end of the esophagus. In the cases in which the tube was not used one ounce of the solution was given every hour during the day and every 2 hours during the night. Usually a sedative was given in the evening. The food consists of small quantities of a bland diet every two hours for twelve hours, milk with one-third cream, cooked cereals (oatmeal, farina, cream of wheat), a soft boiled egg, a slice of toast, butter, cream soups, gelatin, custard, tapioca and junket. For constipation mineral

oil is given daily or enemas every other day. The treatment is employed in cases of hematemesis and melena excepting that the naso-gastric tube is not passed until vomiting ceases but the colloidal aluminum hydroxide is given by the mouth meanwhile and the same diet and sodium phenobarbital hypodermically as a sedative. Small transfusions, 250 cc. are given when the systolic blood pressure is less than 90 and hgb. below 30%.

In three years 407 patients with peptic ulcer were treated with colloidal aluminum hydroxide. There were 322 men and 85 women. The drip method was employed in 270 patients and 86 were on oral treatment. Of these 101 were bleeding on entering the hospital. Twenty-two patients had both gastric and duodenal ulcers, nine had marginal ulcers, six after gastro-enterostomy and three after gastric resection. The most striking features of the treatment are: 1, the prompt relief of pain, 2, the rapid healing of the ulcer, 3, the healing of refractory ulcer, and 4, the excellent results in case of massive hemorrhage, the mortality in the cases being only 3% as compared with 29% in 38 cases in the same hospital in the five year period preceding the inauguration of this form of medical treatment.

Allen Jones, Buffalo.

BENDICK, ARTHUR J.

Early Esophageal Carcinoma.
Am. J. Roent. and Radium
Therapy, Vol. XLI, 603, 1939.

Bendick reports a case of early carcinoma of the esophagus. The importance of this case is that there were only slight burning pains, whenever the patient swallowed hot or cold liquids. The well known symptoms of difficulty in swallowing, bleeding or loss of weight were not present. The routine roentgenographic examination was entirely negative.

Bendick stresses the importance of the examination of the patient in recumbent position. Only in this position the presence of the growth of 1.5 cm. in diameter could be visualized.

Franz J. Lust, New York, N. Y.

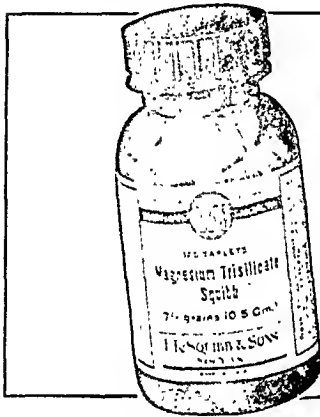
EINHORN, MAX.

The Value of the String Test for the Diagnosis of Peptic Ulcers.
Gastro-enterologia, Vol. 64, p. 65-67, June, 1939.

The string test which was introduced 30 years ago by Einhorn is especially valuable in cases with shallow lesions in the stomach or duodenum, in which a deformity of the stomach or duodenal wall is not present.

Einhorn reports cases of peptic ulcer in which the roentgenological examination of the gastro-intestinal

Antacid of choice in Gastric Hyperacidity



MAGNESIUM TRISILICATE SQUIBB

RECENTLY magnesium trisilicate was proposed for the treatment of peptic ulcers because its sustained antacid and adsorptive effects provide an environment conducive to healing.

Referring to magnesium trisilicate, Mutch¹ (Guy's Hospital, London) states: "Its antacid power is sustained for hours even in the presence of an excess of acid. Not only does this facilitate the continuous control of hyperchlorhydria in the gastric contents as a whole, but it furnishes a basis for a local antacid therapy in the floor of the ulcer itself. In the presence of acid the trisilicate acquires a gelatinous consistency, and if any of the mass lodges in the ulcer crater, it will

¹Mutch, N.: *Brit. M. J.* 1:143, 205, 254, 1936.

progressively neutralize the acid which diffuses through it."

Magnesium trisilicate does not reduce the gastric reaction below the neutral point, nor is it absorbed. Hence there is no possibility of its inducing an alkalosis. Since the general motility of the digestive tract is not disturbed, it does not cause constipation or diarrhea. These features make magnesium trisilicate an antacid of choice in gastric hyperacidity.

Magnesium Trisilicate Squibb is supplied as $7\frac{1}{2}$ gr. palatable, slightly flavored (peppermint) tablets in bottles of 100 and 1000.

Total daily dosage varies between 6 and 24 tablets according to the patient's condition and response.

For literature address the Professional Service
Department, 745 Fifth Ave., New York, N. Y.

E. R. SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

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.....QUITE CONTRARY

TODAY when a child is contrary, nervous, irritable and hard to manage the physician seeks a definite reason. That reason may be dietetic . . . a slight deficiency of some of the vital elements which the growing body needs. Physicians, Nurses and Dietitians well recognize the need for balanced dietaries, and more and more of them are recommending COCOMALT.

COCOMALT HAS "DOUBLE VALUE" . . .

When this malted food dietonic is added to milk the food value is materially increased. The child enjoys the rich full flavor; and COCOMALT acts as an incentive to milk drinking. COCOMALT contains calcium . . . phosphorus, iron . . . Vitamins A, B₁, D and G . . . provides quick energy . . . body building nutrients.

VARIED USES OF COCOMALT

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- Convalescence
- Anorexia
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Please send me the new Dietetic Manual—"A Modern View of Adequate Diet," together with a sample of COCOMALT.

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tract gave no evidence of any lesion. The string test, however, enabled the author to make the diagnosis and proved again to be very valuable.

Franz J. Lust, New York, N. Y.

CUNHA, FELIX.

The Duodenal Syndrome Associated with Aberrant Superior Mesenteric Artery. J. of the Inter. College of Surgeons, Vol. 2, 93, 1939.

Cunha describes the syndrome which is due to an aberrant mesenteric artery. The clinical signs are those of a duodenal ulcer. However, the gastric contents is normal, the

roentgenological examination shows no sign of a peptic ulcer either in the stomach or in the duodenum. Cunha stresses the fact that fluoroscopy however is the most important examination. Roentgenograms cannot possibly demonstrate the condition unless extreme dilatation of the duodenum has taken place. Fluoroscopy reveals the presence of antiperistalsis in the second and third portion of the duodenum, the barium reaching the point of compression at about the terminus of the latter, then being unable to follow through, antiperistaltic waves of muscular action carry it backward to the pylorus, with the production of

an endless churning back and forth between these two points. After some time a secondary dilatation of the duodenum takes place. In those cases in which the syndrome has been present over a long period, absolute stasis in the duodenum is sometimes noted, brought about through fatigue inertia of the smooth muscle. Marked changes in body weight, gross fat depletion or gross fat increase, alter the anatomic relationship and therefore the mechanical function of that region of the duodenum and are apparently an etiologic factor in the occurrence of the described symptom.

Franz J. Lust, New York, N. Y.

GERSTER, JOHN C. A.

Retroperitoneal Chyle Cysts. Annals of Surgery, Vol. 110, No. 3, pp. 389-410, Sept., 1939.

Gerster reports a case of retroperitoneal chyle cyst. The clinical findings were those of a tumor in the right epigastrium. Intensive roentgenological studies enabled the diagnosis of a retroperitoneal tumor pressing on the rear wall of the second part of the duodenum and on the gall bladder. At the operation the tumor was found attached to the anterior aspects of bodies of first and second lumbar vertebrae between the aorta and the inferior vena cava. The aorta was entirely free, but the inferior vena cava was intimately adherent to the right side of the tumor for a distance of three inches. The contents of the tumor was a milky fluid. This tumor was due to a trauma.

Gerster emphasizes that the exact diagnosis is determined by the microscopic character of the cyst wall (lymphangioma, dermoid, hydronephrosis). Analysis of the fluid contents is of secondary interest.

Many cases of chyle cysts are reported under different headings. Gerster's compilation of the literature should be well appreciated.

Franz J. Lust, New York, N. Y.

JUNGNER, G., RYDIN A. AND JOSEPHSON, B.

Elimination of Cholic Acids. II. In Experimental Jaundice. Acta Med. Scand., 97(3/4):254-264, 1938.

The surface adsorption of cholates on the walls of the blood vessels does not occur in obstructive jaundice. The blood cholic acid in animals with toxic hepatitis (after P or CCl₄) was greater than normal but less than that seen in obstructive jaundice, and there is a greater delay in excretion due to injury to the liver parenchyma. Estimation of the blood cholate concentration after injection of Na cholate should therefore furnish a diagnostic liver function test.—J. F. W. (courtesy of Biological Abstracts).

IMPROVE BOWEL RHYTHM in functional constipation WITHOUT IRRITATION!

THE effective answer to the problem of constipation—where irritation or roughage are contraindicated—is the hydrogel, Serutan. Through its unique ingredients, Serutan has a swelling power equal to ten times its own weight. It provides a bland, non-oily, gelatinous bulk to the fecal mass that induces an effective colonic reflex, insuring copious, normal stool elimination.

Serutan is entirely non-irritant, and free from habit-forming drugs or roughage. Clinical tests in hundreds of cases over the past five years have confirmed its efficacy and safety.

The gentle, thorough nature of the peristaltic action Serutan induces indicates its use particularly in spastic constipation, in the constipation incident to pregnancy, colitis, ulcers, hemorrhoids, etc., and for pre- and post-operative use.

Many physicians are now prescribing Serutan because its ability to invoke normal physiologic response provides such a helpful stimulus to intestinal muscle tone. Thus its administration may often be decreased or entirely discontinued after a period of use. Have you tried Serutan in your own costive cases? The coupon will bring professional samples and literature.

Professional Service Division, Jersey City, N. J.

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Gentlemen:

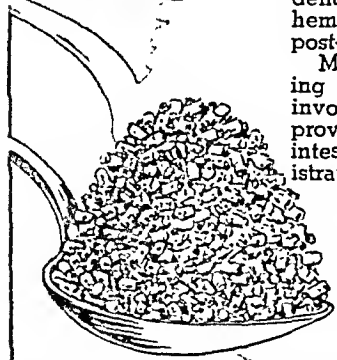
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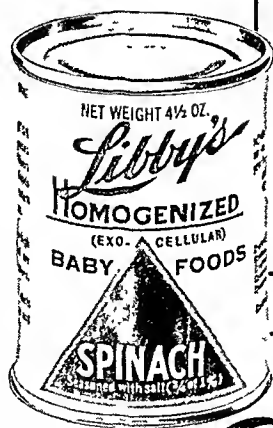
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TO NORMAL
EVACUATION



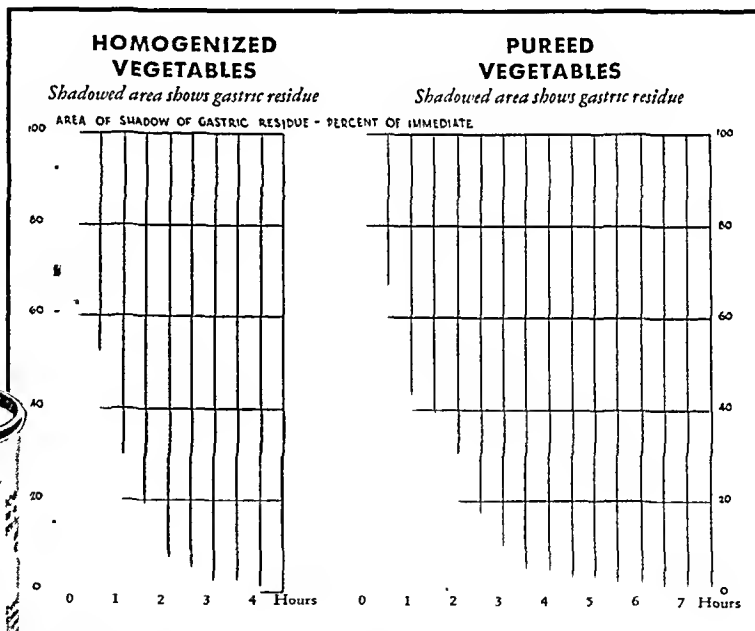
To every doctor
who would like to
supplement a bland diet
with vegetables

THESE CHARTS TELL A SIGNIFICANT STORY

These two charts compare the rates of digestion of homogenized vegetables and pureed vegetables in the stomachs of 8 patients with chronic peptic ulcers. The gastric evacuation time proved to be significantly less for homogenized vegetables (an average of 3.5 hours) than it was for pureed vegetables (an average of more than 5.0 hours).



NOTE: It often seems desirable to add vegetable supplements to the bland diets of patients with functional disturbances of the gastro-intestinal tract—in order to maintain adequate nutrition. At the same time it is essential that the stomach be given both motor and secretory rest. The easy digestibility of specially homogenized vegetables suggested that, in these cases, homogenized vegetables have unusual advantages. To investigate their possibilities, a series of experiments was undertaken. The charts reproduced on this page summarize one phase of these experiments. For a full summary of these experiments (reported in September issue of The Journal Lancet) write Libby, McNeill & Libby, Research Laboratories, Dept. AD-11, Chicago.



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*Libby's specially homogenized vegetables are prepared by an exclusive process that completely breaks up cells, fibers and starch particles, and releases nutriment for easier digestion
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3 Vegetable Combinations
A Fruit Combination
A Cereal Combination
A Nutritious Soup

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3. *Looseness of the bowels.* There are many cases of looseness of the bowel, especially of nervous origin, where Kongsyl by supplying a soft bulk absorbs excessive intestinal fluids and changes loose movements into soft or even formed stools.

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AJ 11-39

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PALMER, WALTER LINCOLN.

Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation. Ann. Int. Med., Vol. 13, No. 2, pp. 317-338, Aug., 1939.

Palmer describes a case of a carcinomatous ulcer of the lesser curvature of the stomach. The roentgenological examination showed it to be a benign lesion. The gastroscopic examination, however, revealed the presence of a carcinomatous ulcer. The histological findings are very well illustrated by the microphotographs. These microphotographs reveal a minute carcinomatous lesion in a fold of the fundus of the stomach. The difficulty of differentiating between benign ulcers and carcinomatous ulcers is emphasized especially in ulcers which show a carcinomatous degeneration. Free acidity of 106 showed after a histamine test. Stool examinations for occult blood varied from negative to strongly positive. Roentgenological examination showed a small gastric lesion. The autopsy showed massive carcinoma metastases to the skeleton. Minute carcinoma metastases to lymph nodes, spleen, and lung.

Franz J. Lust, New York, N. Y.

SCHATZKI, RICHARD.

The Roentgenologic Appearance of Intussuscepted Tumors of the Colon. Am. J. Roent. and Rad. Ther., Vol. XLI, 4, 549-563, 1939.

Schatzki reports eleven cases of intussuscepted tumors of the colon in adults. It is interesting that three of these were pedunculated submucous lipomas, which showed partial necrosis and ulceration. The rest of his cases was due to carcinomata. Schatzki uses mostly the contrast enema and the flat plate. Oral administration of barium is only an additional method.

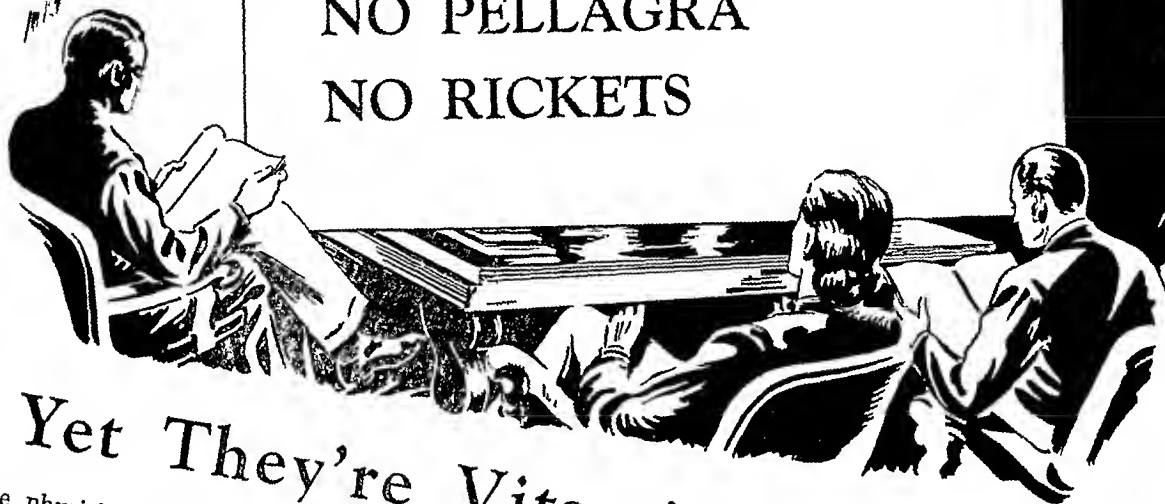
The author discusses the roentgenological signs which differ according to the amount of obstruction and intussusception present. The signs are easily explained by the anatomical process. The barium may enter the central canal as well as the peripheral sheath of the colon. Besides, on the flat film a sausage-shaped, homogeneous shadow (representing the intussuscepted portion of the intestine) can be seen. This area may be surrounded by the air-filled sheath. Occasionally even the tumor can be seen heading the invaginated colon. To differentiate between the fecal matter and intussusception, Schatzki stresses the homogeneity of the pathological shadow, whereas fecal matter has a mottled appearance.

As differential diagnosis we have only to consider (1) the inverted cecum and (2) Kantor's string sign

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of regional ileitis. As to the site, Schntzki differentiates between cecocolic (ileocolic) and colocolic intussusceptions. According to the location only slight differences in the roentgenological aspect take place.

Franz J. Lust, New York, N. Y.

SCHENKEN, JOHN R., STASNEY, JOSEPH AND HALL, W. KNOWLTON.

Lack of Antianemic Principle in Human Liver from Case of Carcinoma of Stomach. Proc. Soc. Exp. Biol. and Med., 40(1): 89-90, 1939.

The injection of an extract prepared from a human liver obtained at necropsy from a patient with carcinoma of the stomach produced no reticulocytic response in a patient with Addisonian pernicious anemia in relapse. The injection of a control extract prepared from the liver of a patient with cerebral hemorrhage caused a marked stimulation of hemtopoiesis. The pyloric and prepyloric portions of gastric mucosa which were replaced by neoplastic tissue in the patient with carcinoma of the stomach have been shown by experimental observations to be most active in the production of the intrinsic factor."—Authors (courtesy of Biological Abstracts).

UPHAM, ROY AND SPINDLER, FRANK.

Studies on Humans with a New Secretagogue Meal. Rev. Gastro-ent., 6(1):12-21, 1939.

The method is too involved for routine gastric analysis. The basis of the test meal is Lumeo meat extract with phenol red indicator. The concentration of phenol red in the test meal is compared with that in the extracted samples. It is claimed that the meal gives "absolute figures" for the amount of HCl produced by the stomach.—G. H. C. (courtesy of Biological Abstracts).

REINERS, HERMANN.

Die Harnstoffbildung in der überlebenden, experimentell geschädigten Leber. Arch. Exp. Path. u. Pharmacol., 190:452-460, 1938.

The formation of urea by the surviving cat liver, removed after poisoning of the entire animal with P, and artificially perfused with blood, was unaltered despite severe changes in the epithelial portion of the liver. Dismantling the endothelial system of the liver with India ink or electrocopper neither checked nor increased urea formation. Simultaneous acute injury to both tissue systems caused a considerable checking of urea formation, even though changes in each system were not as great as had occurred in the injuries of the single systems as studies. Urea formation

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Mucilose Granules, 4 oz. and 16 oz. bottles

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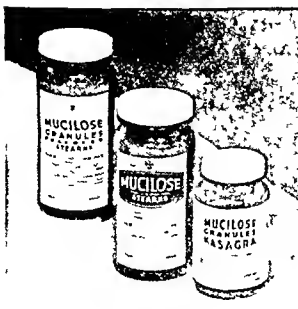
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is not alone a function of the pithelial cells or of the Kupfer star cells; it should rather be considered as a combination work of both tissues. Both the origin and the nature of the injury to the organ are of importance as regards the effects upon this essential function of the liver in diffuse liver pathologies.—C. S. L. (courtesy Biol. Abst.).

STIEBELING, HAZEL K. ANN PHIPARD, ESTHER F.

Diets of Families of Employed Wage Earners and Clerical Workers in Cities. U. S. Dept. Agric. Circ., 507, 1-40, 9 figs., 1938.

This analysis of the quantities of different foods purchased, their cost and their nutritive adequacy, in a relatively well-to-do population group, is based on about 4,000 weekly records, obtained from December, 1934, to February, 1937, in 43 industrial centers in 8 major geographical regions of the U. S. Most of the families were whites; some were Negroes in Middle Atlantic and Southern cities. Median expenditures (whites) ranged from \$2.10 a person a week. (East South Central) to \$2.85 (Pacific coast); of Negroes, \$1.55 (Southern) to \$2.40 (middle Atlantic). Expenditures for food rose with increased economic well-being. Such increments were most pronounced in milk, butter, cream, eggs, meat, fruits, and succulent vegetables, and least for grain products, sugars, and fats other than butter and cream. The average consumption of 36 important groups of foods is given by level of food expenditure and by season, and for 4 regions 194 individual food items are also presented. Comparisons of the average nutritive values of the diets (calories, protein, Ca, P, Fe, vitamin A value, Vitamin B₁, ascorbic acid (Vitamin C), riboflavin, and the pellagrapreventive factor) with suggested daily allowances for each unit are made. The middle 50% of the white families received per requirement unit per day 70-95 gms. of protein; 0.50-0.83 gm. of Ca; 14-17 mgms. Fe; 2,000-4,500 I. U. of Vitamin A; 400-600 I. U. of Vitamin B₁; 50-100 mgms. of ascorbic acid; and 550-900 Sherman units of riboflavin. From 40 to 60% of the diets of white families were in need of improvement, and over 60% of these of Negro families. Most of the diets derived a relatively high proportion of their calories from the flavorful fats, sugars, meat, poultry and fish, a low proportion from milk products, fruits and vegetables other than potatoes. The white families spent from 14-1/2% of their food money for eggs, lean meat, poultry and fish; 3-1/2% for vegetables and fruits; but only 3-1/4% for milk and cheese. For the Negro families the respective figures were 15-1/2% and 3%. Even the good diets fell short of the optimum allowances of protective foods. More emphasis should be put on leafy and green-colored vegetables and upon milk, many of whose inexpensive varieties and forms yield excellent food value for their cost.—Authors (courtesy of Biol. Abst.).

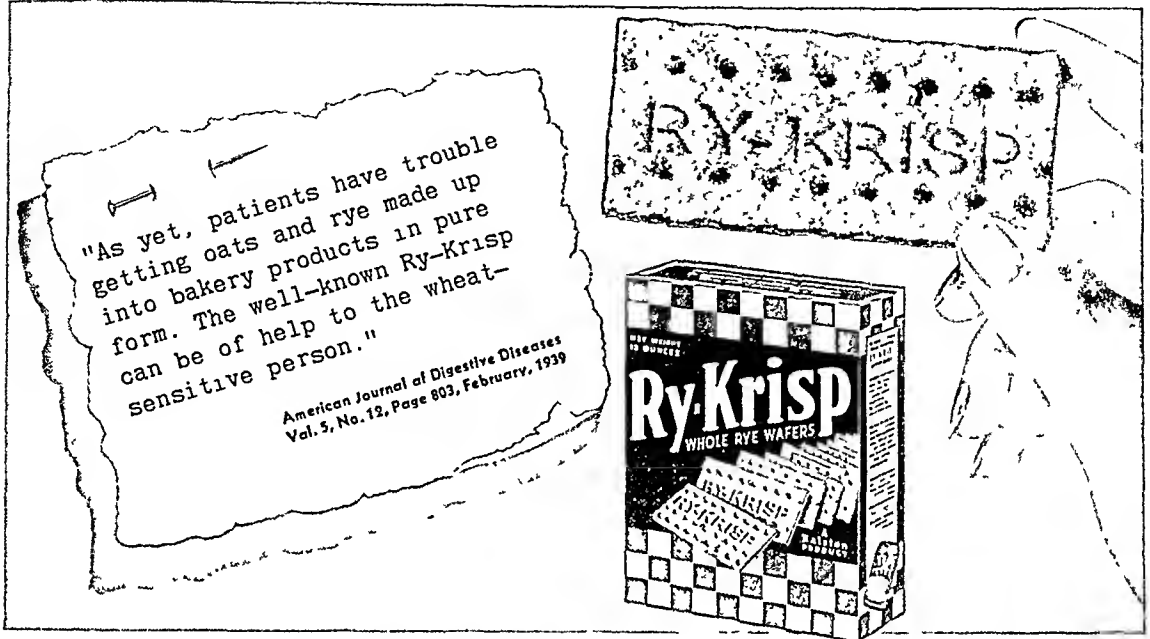
FRUTON, JOSEPH S. AND BERGMANN, MAX.

The Specificity of Pepsin. J. Biol. Chem., 127(3): 627-641, 1939.

Several specific substrates for crystalline swine pepsin were synthesized—such as carbobenzoxy-l-glutamyl-l-tyrosine and glycyl-l-glutamyl-tyrosine. Carbobenzoxy-l-glutamyl-tyrosine was split optimally by pepsin at pH4 into carbobenzoxy-l-glutamic acid and l-tyrosine. Substitution of the free carboxyls in the substrates inhibited pepsin action. Pepsin, an acidic enzyme, therefore required an acidic substrate for its action. The classification of protein-splitting enzymes on the basis of pH optima should be abandoned in favor of a classification on the basis of specificity phenomena. The availability of synthetic substrates for pepsin having only one sensitive peptide bond permits a more precise study to be made of the kinetics of peptic hydrolysis and the quantitative estimation of pepsin in biological fluids. It also permits a comparative study of the relative specificities of pepsins of various animal spp.—Authors (courtesy Biol. Abst.).

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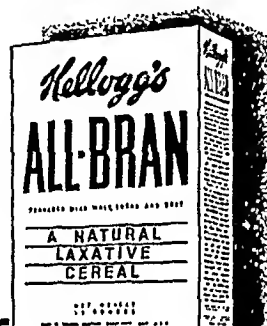
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Obviously, there is no single cause. Each case must be judged on its own merits. Anatomical differences, variations in diet and habit and specific pathological entities all enter into the cause. However, it is safe to say that faulty habit plays a role in the great majority of cases, and that loss of neuromuscular tone is a very common secondary factor.

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*Bulletin 380, The Pennsylvania State College, School of Agriculture and Experiment Station.



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Diffuse Spasm of the Lower Half of the Esophagus*

By

HERBERT W. SCHMIDT, M.D.†
ROCHESTER, MINNESOTA

ESOPHAGEAL occlusion in which an organic lesion is not present at the site of obstruction constitutes a very interesting condition. The better known of such conditions are cardiospasm, localized non-sphincteric spasm and diffuse spasm of the distal half of the esophagus. The last named is the least known of the three conditions and may give rise to a very distressing train of clinical symptoms. For this reason it is indeed essential that we review the anatomic, physiologic and clinical facts concerned with esophageal occlusion. It is the purpose of this paper, therefore, to present such facts, to review typical cases of diffuse spasm, to present a résumé of the clinical and possible etiologic factors responsible and to note the reaction of this condition to various therapeutic agents. For a lucid understanding of the problems concerned in any condition as complex as this, it is well to review first some of the facts as well as some of the controversial points concerning the anatomic and physiologic characteristics of the esophagus.

ANATOMIC CONSIDERATIONS

The esophagus is a muscular tube (1, 2, 3) the proximal portion of which is continuous with the distal portion of the pharynx just posterior to the cricoid cartilage and anterior to the sixth cervical vertebra; it extends caudalward through the posterior mediastinum, through the esophageal hiatus of the diaphragm, and into the abdominal cavity. Its most inferior portion opens into the stomach at a level between that of the tenth and that of the twelfth thoracic vertebra. The mucous membrane is made up of stratified squamous epithelium outside of which there is a thick, tough submucosal layer. The muscularis is composed of an inner circular layer and an outer longitudinal layer, the former predominating in the distal portion and the latter predominating in the proximal fourth. In man, the muscular elements are striated in the proximal third, both striated and smooth in the middle third and smooth in the distal third. Surrounding the muscular coat is a thin fibrous tunica adventitia. The diameter of the esophagus, in general, increases from the proximal portion distalward, the narrowest portion being at the level of the cricopharyngeus muscle. Constrictions are situated also at the level of the aortic arch, the left bronchus and the diaphragm.

The nerve supply is derived from the vagi and the sympathetic chains. Sympathetic fibers are known which come from the inferior cervical ganglia and from the celiac plexus. The existence of direct

branches from the thoracic sympathetic ganglia is still a cause of controversy.

PHYSIOLOGIC CONSIDERATIONS

The function of the esophagus is to convey food and liquid from the oral cavity to the stomach (4, 5, 6, 7). The act of swallowing has been described as occurring in three stages.

Stage 1. After mastication the food is rolled into a bolus and is transported to the pharyngeal entrance by the voluntary action of the tongue and myohyoid muscles.

Stage 2. The mucous membranes of the posterior pharyngeal wall, base of the tongue and soft palate contain sensitive sensory spots, called the chief and accessory spots. These spots are the sites of origin of afferent nerve impulses which are carried over the glossopharyngeal nerve, the second division of the fifth nerve and the superior laryngeal nerves to the center of deglutition in the floor of the fourth ventricle. The impulses thus conveyed institute the second and involuntary act of swallowing. The dependence of deglutition on incoming afferent impulses from special regions in the oral and pharyngeal cavities is illustrated by the fact that deglutition is impossible after thorough cocaineization of the regions in which such impulses originate. Trauma or pathologic processes that affect the center of deglutition make swallowing impossible. This is illustrated in cases of bulbar palsy, amyotrophic lateral sclerosis with bulbar involvement and in certain cases of cerebral thrombosis.

Stage 3. The third stage of swallowing begins when motor impulses are given out from the center of deglutition which set up peristalsis in the esophagus. Three distinct mechanisms exist which control the course of the bolus along the esophagus: (a) The afferent impulse is sent out from the chief and accessory peripheral centers to the center of deglutition in the brain which in turn sends out motor stimuli to different segments of the esophagus to set up peristaltic activity. The continuity of the esophagus is not necessary for this mechanism. (b) The second mechanism consists of a series of reflexes which pass successively through the center of deglutition. Each reflex has its distinct afferent path to the center which in turn sends motor stimuli to definite regions of the esophagus. A bolus of food by its presence locally can precipitate peristalsis. This mechanism is dependent on the integrity of the esophagus as well as on the integrity of the vagus nerves. (c) The third mechanism has been demonstrated by Cannon (8) and Carlson, Boyd and Pearcey (9). After bilateral cervical vagotomy in the cat the entire esophagus is at first paralyzed. Then the part made up of smooth muscle and Auerbach's nerve plexus is capable of local co-ordination independent of afferent or efferent connections with the central nervous system.

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The vagus nerves and sympathetic nervous system innervate the esophagus. It is generally agreed that the vagus system is the chief course for both afferent impulses from and efferent impulses to the organ. The exact details are not yet clearly understood. The role of the sympathetic nervous system is not definitely known but apparently it does not exercise an antagonistic action toward the vagus nerve so far as deglutition is concerned.

Various changes in the esophagus are capable of producing pain. The (5) mucous membrane is not very sensitive to irritants but painful sensations can be felt as arising secondary to spasm and usually are localized in the lower retrosternal and retroxiphoid regions but may be referred into the cervical and mastoid regions, to the angle of the jaw or into one or both external auditory canals. Pain also may be referred to the back at a level between that of the tenth and that of the twelfth thoracic vertebra.

In the study of esophageal motility, tone and spastic phenomena it is well to keep in mind that experimental work will vary according to the animal used, since the anatomic relationship of esophageal musculature, especially the relationship of smooth to striated muscle, differs in various species. The musculature of the esophagus of the dog and rabbit is striated throughout the entire organ. In cats, apes and man the esophagus is composed of striated muscle in the proximal portion and smooth muscle in the distal portion. The goose has an esophagus composed entirely of smooth muscle. Thus the results obtained in laboratory experiments cannot always be directly applied to human beings.

ETIOLOGIC ASPECTS OF ESOPHAGEAL SPASM

From the standpoint of the etiologic basis of spastic phenomena in the distal half of the esophagus interesting and significant experiments have been performed by Carlson, Boyd and Percy (9) and Carlson and Litt (10) on cats and on a *Macacus* monkey. Stimulation of the sciatic nerve produced inhibition of tone at the cardia and distal portion of the esophagus in most of the studies. At times, however, contraction followed sciatic stimulation. The effect was present although both vagi were sectioned in the neck. The state of tone in the distal portion of the esophagus was influenced by thermal, mechanical and chemical stimulation of the tongue and mouth. The state of tone present prior to stimulation was important. If the esophagus was atonic, contractions were noticed when the pharynx was stimulated mechanically. If a high degree of tone was present, inhibition was noticed after pharyngeal stimulation. Similar effects were noticed when the central portion of the glossopharyngeal nerve, created by division, was stimulated. These reflexes failed to occur after section of the vagi. Traction on intact vagus nerves, sudden stretching of the stomach, mechanical stimulation of the gall bladder or common bile duct caused severe hypertonus or spasm at the cardia. It was felt that both vagi and splanchnic efferent pathways were involved in these reflexes, since they were obtained in a diminished degree after section of both vagi but were not obtained after section of both vagi and splanchnic nerves.

Strong distention or compression in the urinary bladder, large or small bowel, or cutaneous stimulation produced prolonged contractions or spasm at the cardia. The authors felt that long reflex mechan-

isms apparently could be thrown into activity by the stimulation of any sensory nerve in the body.

Veach (11) stimulated nerve fibers peripheral to the celiac ganglion and the splanchnic nerves in cats and observed more or less maintained tonic contractions on which rhythmic contractions were superimposed in the distal portion of the esophagus in both cases.

The results of the aforementioned experiments are interesting when one speculates as to the etiologic basis of diffuse spasm of the esophagus. Moersch and Camp (12) postulated as to the possibility of reflex origin. Schultz Ortiz (13) and Einhorn and Scholz (14) have called attention to conditions which may precipitate reflex spasms in the esophagus. These spasms may be secondary to lesions within the esophagus itself as in the case of carcinoma, esophagitis or foreign body. They may be secondary to lesions within the stomach such as carcinoma, gastric ulcer or diaphragmatic hernia. They may be secondary to lesions in the gall bladder or biliary tract. Esophageal spasms have been described which have been due to organic disease of the central nervous system, as the result of poisoning with lead, arsenic and belladonna, or in the course of infections or tetany. Sluder (15) observed nonsphincteric spasm of the esophagus in a case in which a positive Wassermann reaction was obtained. The esophageal spasm disappeared after cocainization of the sphenopalatine ganglion. Eloesser (16) has presented four cases of persistent nonsphincteric spasm of the esophagus occurring at the level of osteoarthritic deformities of the spine. Disturbance of innervation secondary to pressure was postulated as being a possible cause.

As can readily be seen, it is extremely important that a primary pathologic process in the esophagus and elsewhere in the body be searched for when any individual has diffuse esophageal spasm.

Comby (17), Jacobson (18, 19), Muggia (20), Brühl (21), Sudhues (22) and Schultz Ortiz (13) have observed cases wherein emotion apparently alone has precipitated rather severe esophageal spasms. It has been our experience to find that in some cases of diffuse spasm of the esophagus emotion plays a definite etiologic part.

CLINICAL SURVEY

A clinical survey of diffuse spasm of the distal portion of the esophagus is interesting but difficult.

Historical. Probably the first description of diffuse spasm of the esophagus was made in 1889 by Osgood (23) who read a paper before the Boston Society for Medical Improvement wherein he told of six cases in which there must have been severe esophageal spasm. All of these patients complained of dysphagia. His description of symptoms was as follows: "The distress was always located beneath the xiphoid cartilage as high as its union with the gladiolus, and here tenderness on pressure is usual. From its point of origin the discomfort, which is very peculiar in character, may radiate up to the pharynx and from that locality pass into one or both ears. . . . When the entire tract of the esophagus is thus involved the distress is very annoying and is apt to alarm the patient. . . . There is the sense of impending suffocation. . . . Sometimes the distress appears to the right of the median line and gradually involves the right chest as far as the outer

border of the mamma, being sharply felt in the nipple. In extreme cases pain is felt in the back. . . At all times there existed difficulty in swallowing beer, champagne, apollinaris water, and other gaseous drinks. As soon as the fluid reached the lower end of the esophagus a spasmodic, but only momentary, constriction followed. . . It is during the existence of an obstinate attack that the sufferer complains of a strange sensation of pain in one ear, very rarely both ears, and not at all in some cases. . ."

Osgood (23) remarked about the unusualness of this syndrome, in that there was "no absolute stenosis" of the esophagus. Unfortunately the diagnosis could not be established accurately due to the fact that roentgen rays had not been known at that time. More recently with accurate roentgenologic examinations of the esophagus diffuse spasm was probably recognized by Teschendorf (24) and by Bársony and Polgár (25), but it remained for Moersch and Camp (12) to describe this condition as a distinct clinical entity.

Diffuse spasm of the esophagus is generally characterized by dysphagia and pain. The dysphagia is intermittent in character at the onset. The point of obstruction is usually situated dorsal to the distal half of the sternum. Variation as to the type of food or liquid which precipitates dysphagia and pain is noticeable. The condition may go on to complete esophageal obstruction which lasts variable lengths of time. This complication may be so severe that a gastrostomy may be necessary. Pain is frequently a very distressing symptom. The pain may simulate that of angina pectoris, or of disease of the stomach or gall bladder. In several instances incorrect diagnoses have been made and thus specific therapy has been directed toward a condition which did not exist. Pain may vary from a dull sense of discomfort to a sharp excruciating pain which may simulate gall stone colic in its severity. Pain is usually situated in the retro-xiphoid and retrosternal region but may extend to the back in the neighborhood of the tenth and twelfth dorsal vertebrae or may extend upward along the anterior portion of the thorax into the cervical region and into the external auditory canals and then along the jaw. Pain may be precipitated by meals or it may occur independent of the ingestion of food or liquids since attacks of pain have awakened from a sound sleep individuals who have this difficulty. Almost all patients who have diffuse spasm of the esophagus are of an intense, temperamental makeup. Invariably exacerbations are precipitated by nervous strain, nervous fatigue or anxiety.

Moersch and Camp (12) have described very clearly the roentgenologic changes seen in cases of diffuse spasm of the esophagus. It is desirable that roentgenoscopic observations be performed, because roentgenograms represent only certain phases of the entire picture. Three main types have been listed according to the findings on roentgenoscopic examination: (1) diffuse, irregular spasm in the distal half of the esophagus; (2) multiple spastic segments and (3) diffuse narrowing of the distal half or third of the esophagus. The type may vary in degree and at times during the examination the different types of spasm may occur in the same individual. As barium is swallowed there are rapid changes in the size of the esophageal lumen due to irregular peristalsis. The barium moves up and down with peristalsis. From time to time part of the barium mixture is allowed to

enter the stomach when the distal end of the esophagus dilates slightly. Attention was called to the fact that in the distal end of the esophagus there is a rapid change in the size of the esophageal lumen in contrast to the fixed defect of cardiospasm. Another striking feature of diffuse spasm which helps to distinguish it from cardiospasm is the relatively small degree of dilation that occurs proximal to the involved portion, regardless of the duration of symptoms. In cases of cardiospasm, dilation of the esophagus proximal to the cardia is usually severe.

In some cases the spasm may cause the appearance of multiple regions of regular, concentric narrowing, between which regions portions of the esophagus have the appearance of diverticula. The true nature of the condition is made clear by roentgenoscopic examination.

Esophagoscopy examination of patients who have esophageal spasm may be somewhat difficult because of the nervous instability of many of these patients. There is marked spasticity of the esophagus in the affected portion, the lumen may appear as a dimpled area. Usually, however, by taking an adequate amount of time and without using force, the esophagus will relax and it is possible to introduce the esophagoscope into the stomach. If a cannulated sound is passed over a previously swallowed silk thread spasm in the distal portion of the esophagus can be felt to offer an increased elastic resistance. At times the spasm is so extreme that it is impossible to pass a sound beyond the involved portion. The degree of spasm may vary from day to day, a fact already established by the roentgenologist. At times the passage of a sound is accompanied or followed by pain which is similar to the pain which causes the patient to consult the doctor.

Treatment. An adequate therapeutic regimen for patients who have diffuse spasm of the esophagus is as yet lacking. It is desirable that these individuals avoid fatigue, too much nervous strain and anxiety. Emotional upsets can precipitate exacerbations of the condition. Under an adequate amount of mental and physical relaxation improvement usually occurs.

Esophagoscopy. Diagnostic esophagoscopy gives certain individuals partial relief. At times this procedure has given more relief than dilation by means of sounds that have a larger diameter than the esophagoscope.

Dilation. Dilation is accomplished by the use of sounds and the hydrostatic dilator. These cannulated instruments are passed over a previously swallowed twisted silk thread. Improvement is usually effected but the results are in no respect so striking or satisfactory as the results achieved in cases of cardiospasm.

Drugs. Many drugs have been suggested for the relief of esophageal spasms. Perhaps the most widely used drugs in the past have been atropine and belladonna. Unfortunately, the results have not been uniformly satisfactory. Guns (26) found that atropine caused prolongation of the passage of a bolus through the esophagus. Howarth (27), Guns (26), Doumer and Cuvelier (28) reported good results with the use of papaverine in treating spastic conditions of the esophagus.

The value of having suitable drugs to aid individuals who have diffuse esophageal spasm during an exacerbation is quite evident. For this reason a series



Fig. 1. The effect of morphine sulfate, intravenously, on esophageal contractions; from a case of diffuse spasm of the distal third of the esophagus.

of studies to determine the effect of various drugs on the smooth muscle of the esophagus were conducted by Dr. John McGowan and me (29).

EXPERIMENTAL STUDY

A soft rubber balloon was connected to the distal end of a perforated Sawyer tube. This system of balloon and tube was made airtight and watertight, leaving only the proximal portion of the Sawyer tube open to be connected with a pressure recording device. The pressure recording device was made up of a water manometer with the distal column of water supporting a float with a writing point. A smoked drum was used to record changes of pressure within the system. The balloon and tube were swallowed by the experimental subject and placed in the distal third of the esophagus. Determination of its situation was made by roentgenoscopic examination after the balloon was in place and partially filled with iodized oil. The experiments were conducted with 12 cc. of water in the balloon-tube system. If too much fluid was used esophageal contractions became very active and very difficult to record on the smoked drum. The system was then connected to the recording apparatus. Soon after introduction of the balloon and tube great esophageal activity was observed. This activity was allowed to subside before the studies were started.

RESULTS

Morphine sulfate. Morphine sulfate given intravenously caused prompt and definite relaxation of the smooth muscle in the distal third of the esophagus both in normal individuals and patients who had diffuse spasm of the distal half of the esophagus (Fig. 1).

Amyl nitrite. Amyl nitrite when inhaled caused great temporary relaxation of the distal portion of the esophagus. This effect occurred in normal individuals as well as in patients who had diffuse spasm of the esophagus (Fig. 2).

Benzedrine sulfate. Fifteen milligrams of benzedrine sulfate given through a Sawyer tube to a patient who had diffuse spasm of the esophagus caused a severe drop in intra-esophageal pressure. The esophagus remained quiet for about an hour after which there was a severe increase in esophageal contractions with a severe rise in intra-esophageal pressure which persisted until the experiment was discontinued fifty minutes later because of pain. The patient stated that retrosternal and retroxiphoid pain caused by esophageal spasm could be felt at least two hours after the experiment was discontinued.

Benzedrine sulfate given to normal individuals did not produce any definite effect on the distal portion of the esophagus.

Fifteen units of insulin were given to a normal individual. During the hypodermic injection there was a drop in pressure in the balloon which lasted sixty-four seconds. After fifty-five minutes esophageal contractions became less frequent and finally ceased. During this period the subject experienced definite symptoms of hypoglycemia. During this entire period in which symptoms of hypoglycemia were present there was a rather severe degree of relaxation of the esophagus. Adrenalin, aromatic spirits of ammonia, sodium nitrite, mecholol, metrazol and trethylene



Fig. 2. Relaxation of esophagus of normal person after inhalation of amyl nitrite.



Fig. 3. Severe, diffuse spasm of the esophagus; the gastrostomy tube is shown.

showed no definite tendency to cause relaxation in the distal third of the esophagus.

The results after subcutaneous administration of atropine sulfate were variable. In some of the experiments a severe degree of relaxation was noted but at other times effects could not be observed.

REPORT OF CASES

Between January, 1935, and September, 1938, seventeen patients who had diffuse spasm of the distal half of the esophagus were seen at The Mayo Clinic. Five representative cases will be presented.

Case 1. A white man, sixty years of age, stated that he had had dysphagia for two and a half years before registration at the clinic. He had experienced the "sticking" of food in the lower retrosternal region. His greatest difficulty had been with tap water and salt mackerel. At times he had regurgitated food but at no time had he experienced pain. Two years before coming to the clinic complete esophageal obstruction had developed, and a gastrostomy had been done elsewhere. Since that time he had found it necessary to take almost all food through a gastrostomy tube. Dilatation and esophagoscopy had been performed many times without benefit.

On admission to the clinic, roentgenologic study revealed diffuse spasm of the distal half of the esophagus (Fig. 3). Esophagoscopy revealed that the esophagus was severely spastic. This change was most prominent in the distal third. An organic lesion could not be demonstrated in the esophagus. A detailed history was taken and an examination for some primary condition which might cause reflex spasm was performed. The only significant facts were as follows: (1) In 1920, cholecystectomy had been performed elsewhere, presumably for cholecystitis; (2) the patient had been troubled with bronchial asthma for two years and (3) carious teeth were present.

Novocain was injected in the cervicodorsal region, after which the patient was able to swallow ice water without

difficulty and barium was seen to pass into the stomach. On the basis of the definite improvement which occurred after cervicodorsal sympathetic anesthesia, a bilateral cervicodorsal sympathetic ganglionectomy and trunk resection was performed. After operation the patient was able to eat everything for fifty-two hours and then the esophagus became closed completely. The esophagus was subsequently dilated by means of sounds. Improvement was not noted for a year and a half; then swallowing improved in a remarkable manner until at present he has very little trouble. At times he can eat any food without a bit of trouble. Use of the gastrostomy tube was discontinued more than nine months ago.

Case 2. A white man, fifty-three years of age, had noticed dysphagia for the first time, in 1930, while drinking a beverage that contained caffeine. Soon afterward, dysphagia had developed in relation to solid food and liquids other than this beverage and more recently, a burning sensation had developed in the lower retrosternal region after swallowing solid food. At times, by taking plenty of time and by drinking plenty of water with his meals he had experienced very little trouble. Occasionally, while lying down he had heard "a fizzing sound" coming from the retrosternal region. He had been a heavy smoker, smoking ten to fifteen cigars a day, and had been in the habit of drinking excessive amounts of a beverage containing caffeine each day. He had stopped drinking this beverage and stopped smoking with noticeable improvement in his symptoms. He had been nervous and irritable for the two years previous to registration at the clinic.

Roentgenologic studies showed a severe diffuse spasm of the distal half of the esophagus (Fig. 4). Esophagoscopy was rather difficult to perform because of severe spasm of the distal third of the esophagus. An organic lesion was not visualized. The rest of the examination gave negative results. The patient was given sedatives and was advised



Fig. 4. Multiple spastic segments in the distal half of the esophagus.



Fig. 5. Diffuse spasm of the distal portion of the esophagus.

to avoid too much nervous strain. Recent information regarding his condition is not available.

Case 3. A Jew, aged fifty years, stated that for one year he had had dysphagia. His trouble had begun with solid foods only but soon liquids were found to cause trouble also. At times he could take liquids without any trouble but at other times he would have considerable difficulty with them. He had lost twelve pounds in a year. Roentgenologic studies of the esophagus, performed elsewhere, showed "an ulcer of esophagus."

He came to The Mayo Clinic in May, 1938. The results of physical examination were negative. Roentgenoscopic examination showed spasm at the cardia with diffuse spasm of the distal part of the esophagus (Fig. 5). Other studies, including roentgenologic examination of the stomach and duodenum and routine laboratory tests, gave negative results. A half grain of papaverine was prescribed to be taken three times a day, one-half hour before meals. This was taken for two days and had very little effect on deglutition. The esophagus was then dilated to the size of a No. 41 French sound and 1 grain of stramonium was given twice a day. After four days the patient was able to eat anything without trouble. He was allowed to return home taking 1 grain of stramonium two times a day for two weeks out of four.

Case 4. A white woman, fifty years of age, stated that she had been troubled with belching, flatulence, "sour stomach" and "pressure" in the upper part of the abdomen immediately after eating. Foods such as cabbage, apples, fatty or fried foods and tomatoes had particularly caused trouble. She had noticed definite dysphagia when excited or nervous. At times this had become so severe that she was unable to swallow water. At times she had regurgitated food and liquids.

A tumor about three times the size of a normal uterus was found in the left adnexal region on physical examination. This was believed to be an ovarian cyst. Roent-

genoscopic examination revealed a diffuse spasm of the distal portion of the esophagus (Fig. 6). Roentgenologic examination of the gall bladder, stomach and thorax gave negative results; gastric acid values were: free hydrochloric acid 40, total acidity 52. The basal metabolic rate was minus 12. The routine laboratory tests gave normal results. The esophagus was dilated to the size of a No. 41 French sound after which she was able to swallow better than formerly. An exploratory pelvic operation was advised but was postponed due to the illness of her husband.

Case 5. A white woman, aged seventy years, complained of having experienced rather severe dysphagia since March, 1937. At the onset the dysphagia had been mild but after a period of two weeks, she had experienced severe obstruction of the distal portion of the esophagus. At times she had had rather severe crampy, colicky pains in the superior portion of the epigastrium and in the inferior portion of the retrosternal region. This had been partially relieved by heat. The degree of dysphagia had been variable. At times she had experienced very little trouble and at other times had been able to eat only thin gruels and liquids. She had lost seventy pounds in seventeen months. Her family physician very keenly had observed a spasm in the distal part of the esophagus and had suspected the presence of an intrathoracic tumor.

Physical examination revealed that essential hypertension was present. The blood pressure was 188 mm. of mercury, systolic and 110, diastolic. Roentgenologic studies showed diffuse spasm of the distal half of the esophagus (Fig. 7). Roentgenologic studies of the gall bladder and stomach gave negative results. Routine roentgenologic examination of the thorax revealed calcification and torsion of the aortic arch. The esophagus was dilated to the size of a No. 45 French cannulated sound by passing it over a previously swallowed silk thread. There was considerable spasm felt in the distal part of the esophagus. Stramonium was prescribed but gave no definite relief. Papaverine hydrochloride, 3/4 grain was prescribed to be taken



Fig. 6. Diffuse spasm of the distal portion of the esophagus.

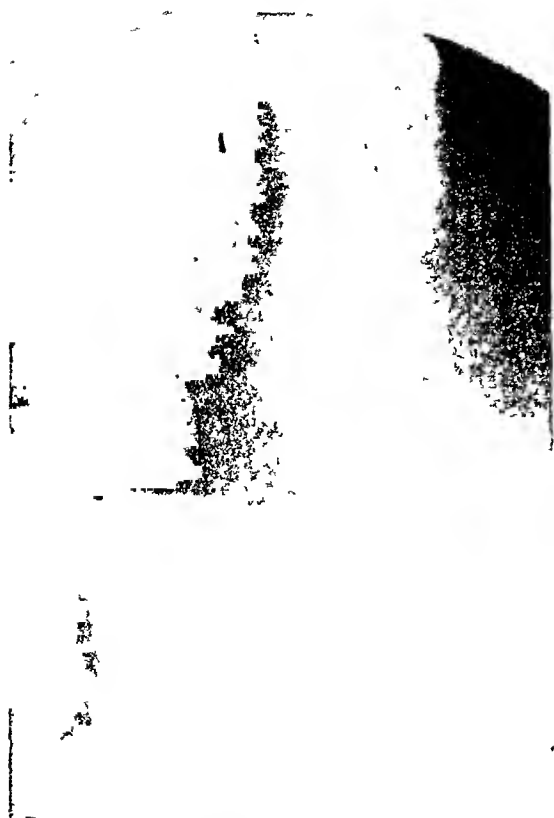


Fig. 7. Diffuse spasm of the distal portion of the esophagus.

a half hour before meals three times a day. The patient stated that this gave a great deal of relief.

COMMENT

In fifteen of the seventeen cases of diffuse spasm of the esophagus encountered at The Mayo Clinic between January, 1935, and September, 1938, this condition was the primary chief complaint. Seven of these patients were women and eight were men. The youngest patient was thirty-one years of age and the oldest, seventy. Other conditions were found in certain cases of the group which might have been partly responsible for the esophageal spasm. These conditions were diverticula of the distal portion of the esophagus, duodenal ulcer, duodenal diverticulum, chronic cholecystitis with cholelithiasis and a pelvic tumor. One patient had asthma, one had diabetes mellitus and one complained of sore gums secondary to dental extraction. Objectively, morphine sulfate and amyl nitrite caused relaxation of the distal part of the esophagus and subjectively, certain patients were helped by the use of stramonium, and others by the use of papaverine.

Two additional patients who showed evidence of diffuse spasm of the distal portion of the esophagus were seen at the clinic during the same period in which the aforementioned cases were observed. Both of these patients came because of serious organic heart disease. One man had had repeated coronary occlusions and had severe hypertension. He stated that cold liquids caused dysphagia and regurgitation.

A second man had severe coronary disease and heart block.

Many highly nervous individuals were seen who complained of transient dysphagia but whose entire examination, including roentgenoscopic examination of the esophagus, gave negative results. These cases were not included in the series.

SUMMARY

It is the purpose of this paper to call attention to a group of cases of esophageal occlusion in the distal portion due to diffuse spasm. A brief review of the facts and controversial points concerning the anatomic and physiologic characteristics of the esophagus is presented. It is of interest to note that spasm of the distal portion of the esophagus can be produced experimentally by the stimulation of various nerves. Spasm has been observed clinically secondary to organic lesions of the esophagus, stomach, gall bladder and biliary tract and in cases of organic heart disease. Spasm of the distal part of the esophagus occurs among certain nervous individuals when they are placed under emotional strain.

Diffuse spasm of the distal half of the esophagus is a condition which is usually characterized by dysphagia and pain. The condition may go on to complete esophageal obstruction. The pain may resemble that caused by disease of the stomach or of the gall bladder or by organic heart disease and for these reasons an incorrect diagnosis may be made and, thus, treatment may be directed toward a condition which does not exist. Pain at times is very severe and is usually situated in the lower retrosternal region but may extend to the epigastrium, to the back, into the neck or ears or to the angle of the jaw.

The roentgenoscopic examination is very important in this condition. Three main pictures have been described: (1) diffuse irregular spasm, (2) multiple spastic segments and (3) diffuse narrowing of the distal half of the esophagus. This is definitely different from that of cardiospasm. Esophagoscopic examination shows evidence of spasm in the distal half of the esophagus.

Satisfactory treatment for this condition has not been evolved as yet. It is important that fatigue, nervous strain, anxiety and emotional upsets be avoided, for they almost invariably precipitate an exacerbation of symptoms. Most of the individuals who suffer from this condition are tense and nervous. Esophagoscopy and dilation of the esophagus by means of sounds and the hydrostatic dilator may give partial relief but the results of dilating the spastic esophagus are in no respect so striking or so satisfactory as they are in cases of cardiospasm.

A method for studying esophageal contractions and the effect of various drugs on the distal portion of the esophagus has been described. Objectively a decrease of tone and of contractions was observed after inhalation of amyl nitrite. The effect was great but transitory. This effect has been observed through the esophagoscope in cases of diffuse spasm of the distal portion of the esophagus. Morphine sulfate intravenously caused rather severe, prolonged relaxation of the distal portion of the esophagus. The administration of atropine sulfate gave conflicting results.

Seventeen cases of diffuse spasm of the lower portion of the esophagus were studied. Possible

primary causative conditions are listed and include traction diverticula of the distal portion of the esophagus, duodenal ulcer, diverticulum of the duodenum, gall bladder disease and organic heart disease. Subjective improvement was observed after esophagoscopy and esophageal dilation as well as after the use of certain drugs such as stramonium and papaverine.

CONCLUSIONS

1. Diffuse spasm of the distal portion of the esophagus is a condition which as yet is not clearly understood.

2. Roentgenoscopic findings associated with this condition are very definite.

3. It is possible for intra-abdominal and intrathoracic pathologic conditions to cause reflex spasm in the distal portion of the esophagus.

4. It is possible for emotion to precipitate spasm of the distal portion of the esophagus in certain nervous individuals.

5. An entirely satisfactory treatment for diffuse spasm of the esophagus is lacking as yet. Partial relief of symptoms can be secured in some cases by means of esophageal dilation.

6. Amyl nitrite and morphine sulfate cause relaxation in the distal portion of the esophagus in objective studies. The action of atropine on the esophagus is not conclusive.

7. Subjectively some individuals received relief of symptoms after the administration of stramonium and papaverine hydrochloride.

8. Need for further study of this condition is evident in order that we may have a fuller concept as to its cause and management.

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The Problem of Gastric Hyperacidity*

By

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THE term hyperacidity has been used to designate (1) highly acid gastric juice, (2) a very free flow of gastric juice, usually of high acidity, and (3) a group of clinical symptoms, namely, fullness, distress and burning in the epigastrium, at times associated with the regurgitation of "acid" material. It is often stated or implied that the very sour stomach secretion is responsible for the symptoms. We wish briefly to criticize the above concept, but to point out that pathological hyperacidity does in fact occur under special conditions.

Confusion in the subject goes back for many years; indeed, ever since it has been known that the stomach produces acid alleged disorders of secretion have been related to unpleasant symptoms. But most of these

views were based on inadequate or erroneous data. Hilton Fagge, in 1886, representing the best English practice of the time, was apparently unfamiliar with actual measurements of gastric secretion but he refers to "another form of gastric pain" which "begins two to four hours after a meal and lasts for several hours. This writer thought that its seat was in the duodenum. But Sir Thomas Watson points out that one can generally remove it by giving an alkali. . . He therefore supposes that it is due to the continued secretion of gastric juice after the food has passed through the pylorus" (1). By 1894 William Pepper in America was familiar with clinical methods of measuring gastric secretion and, following the German writers, especially Leube, was inclined to relate symptoms to variations of the stomach juices. As regards "nervous dyspepsia" for example he found that "in

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the form which is combined with hyperacidity there is a burning, gnawing pain in the stomach, thirst and sometimes sour eructations, and even vomiting of acid liquid" (2). There was no doubt in his mind that symptoms were due to excessive acidity "for, although the prime factor is, of course, a neurosis, the actual cause of the pain is the local irritation of the terminal filaments of the pneumogastric nerves in the stomach by the acid." It is of interest that despite these views Pepper does not mention alkali as a method of treatment but advises arsenic, nitrate of silver, valerianate of zinc, cocaine, Hoffman's anodyne, hydrocyanic acid and chloroform. "The local application of the galvanic current has proved valuable even in obstinate cases." Coming on to 1914 the situation is not clarified by the information given in Emerson's Text Book on Clinical Diagnosis. The old error of setting up rigid limits of normality is maintained when it is stated that "one hour after the Ewald breakfast the total acidity averages normally 40 to 60 per cent, or 0.15 to 0.22 per cent HCl; over 0.25 per cent means hyperacidity" (3). If one applies this concept literally a person with total acidity of 60 would be normal, one with total acidity of 61 would have hyperacidity, an abnormal state; and the whole subject is clearly reduced to absurdity. By 1930 doubt was being cast on the older views but McCrae in Osler's Practice still felt that there are "some symptoms apparently associated with hyperacidity. . . . There is a sense of weight and pressure, with burning in the epigastrium, commonly associated with acid eructations" (4).

The few examples which have been given above to illustrate the confused state of the subject could be multiplied indefinitely; suffice it to say that even at the present time physicians frequently speak of the syndrome of epigastric distress and burning as "hyperacidity" just as they refer to concentrations of gastric acid above certain arbitrary values as hyperacidity. It is evident, then, that certain data are necessary to clarify the question; first the full range of secretion in normal people, both as to acidity and quantity, must be established; and secondly, it must be determined whether the alleged symptoms of "hyperacidity" are directly related to the degree of acid of the gastric juice.

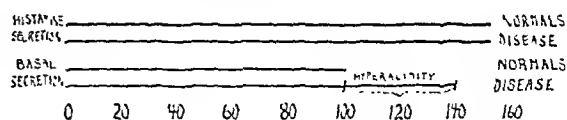
Pollard and Bloomfield in 1931 (5) using a standard histamine test measured the gastric secretion of people who had no evidence of stomach disorder and found that the total acidity varied from 30 to 150. It may be recalled that the latter figure approaches the upper limit of acidity which the stomach is capable of attaining, pure acid gastric juice, according to physiological studies, having a concentration of 0.170 N (6). It is true that the majority of the people in our normal series had a total acidity in the vicinity of 110 to 120, but exceptions were frequent at both ends of the distribution curve. Studying the quantity of gastric secretion in the same group it was found that the highest ten-minute output after histamine stimulation varied from 8 cc. to 70 cc. even though one-half of the determinations fell within the limits of 21 to 35 cc. Pollard in 1933 (7) elaborated the above observations and was able to report on histamine tests in 654 normal people. These studies were adequate for the setting up of definitive standards and fully confirmed the previous smaller series.

Pollard's series of normal people was supplemented by histamine tests on 166 patients with peptic ulcer.

Although it is notable that the most acid and profuse gastric secretion encountered in the clinic is found in patients with peptic ulcer, in no case were the limits established for normals transgressed. It is clear then that inasmuch as the entire possible range of gastric acidity is found in normal people, one may speak of relatively high or low acidity in relation to the frequencies revealed by the distribution curve, but *hyperacidity* is an inaccurate and misleading term, implying as it does disease or at least a state of pathological physiology.

Such are the facts when gastric secretion is explored with the powerful stimulus of histamine. It seemed possible, however, that under other conditions true "hyperacidity" might be demonstrated and this was actually the case when spontaneous or basal gastric secretion was investigated. Basal secretion, briefly, is measured by aspiration of gastric juice in subjects at rest under basal fasting conditions as if prepared for a metabolism test. The total juice is collected over successive ten-minute periods for an hour or more until a steady level of secretion is reached. For further details the paper of Pollard and Bloomfield (8) may be consulted; suffice it to say that such basal secretion reflects the spontaneous influence of autonomic nerves as well as possible intrinsic or humoral secretory stimuli and is to be distinguished from juices produced by histamine or food stimulation. Detailed studies of basal secretion will be published elsewhere, but in the present connection it need only be emphasized that as with histamine juice a wide range of acidity is encountered although the values, on the whole, are of course lower than after histamine. In some 75 people without evidence of organic disease of the stomach the basal total acidity varied from a few degrees up to 97. One patient with Raynaud's disease had a value of 111 and two patients with "indigestion" but no abnormal X-ray findings, had acidities of 110 and 117. As far as our present experience goes one may, therefore, place the upper limit of basal total acidity at approximately 100; it is certainly not over 120. Turning, however, to patients with proven organic disease of the stomach, notably duodenal ulcer, basal total acidity as high as 140 was encountered. Indeed among a consecutive series of 26 cases of duodenal ulcer basal acidity of over 100 was found in 14 and acidity of over 120 in 8. Basal or spontaneous gastric secretion may then exhibit a truly pathological degree of hyperacidity, that is to say a higher acid than is ever met with in normal people under the same conditions of testing. (See Chart 1). The volume of basal

CHART 1
RANGE OF ACIDITY IN



gastric secretion showed similar interesting relations. The output per ten-minute period in the normals rarely exceeded 15 cc., whereas among those just mentioned with hyperacidity there were three who secreted 30 cc. or more and eight with ten-minute volumes of over 20 cc. While the highest levels of

acid and volume do not always coincide in the same individual the tendency to a coincidence of hypersecretion and hyperacidity is striking.

The pathological hyperacidity and hypersecretion described above was not necessarily associated with any symptoms and this brings us to a discussion of the second aspect of the problem. Are there any specific symptoms directly due to highly acid gastric secretion? Is the clinical syndrome loosely spoken of as hyperacidity in fact due to a disorder of secretion?

It may be said in advance that a good many physicians simply assume that a "burning" sensation in the epigastrium is due to acid. Acid burns, hence a burning feeling is caused by acid. That this assumption is, however, not necessarily true is shown by very simple experiments. If a small balloon is placed in the esophagus and inflated an unpleasant sensation results. Although all possibility of participation of acid in the genesis of this sensation is eliminated, complaint of a burning feeling is frequently made by the patient. In our series (9) of inflation experiments such statements as "a deep burning," "a prickly pear down there," "finger nail against a hot stove," "sharp burning," or "burning, gnawing pain" were mentioned by the subjects. Similarly, inflation of the stomach produced such complaints as "burning sickish feeling as when he overeats," and with duodenal inflation "a hot sticking pain," "a burning cramp," etc., were mentioned. Furthermore, inflation of stomach or duodenum in patients with indigestion often reproduced their spontaneous discomfort. It is clear, then, that the assumption that burning sensations are due to burning by acid is unwarranted. Further clinical evidence is the occurrence of "burning" indigestion in some people with complete gastric anacidity. Conversely, as we have pointed out above, it is common to have high levels of gastric acidity without any clinical symptoms at all. The relief of "burning" by soda has been emphasized as proof of symptoms being due to acid, but as we have shown elsewhere (10) such relief

can not be explained by simple neutralization of acid, but it is necessary to assume an alteration of stomach tonus as a result of liberation of gas in the stomach. Finally it must be recalled that indigestion is often relieved by relaxing strain, correcting faulty eating habits and by other measures which produce no alteration of gastric acidity. In brief, all the evidence indicates that symptoms of so-called hyperacidity are due not to acid but to abnormal states of spasm or tension of the stomach or duodenum.

It is of course true that many people with indigestion have high gastric acidity and vice versa. That these two phenomena—hypertonus and hypersecretion—are both the common effects of a certain type of autonomic nervous system rather than one the cause of the other seems to us self-evident, just as glycosuria and acidosis are the common effects of a disorder of metabolism, neither being the cause of the other.

SUMMARY

It may be concluded that the clinical syndrome of so-called "hyperacidity" is spurious in so far as there is no evidence that acid plays a direct part in producing the symptoms. As a clinical designation the term hyperacidity should be abandoned as inaccurate and above all misleading, since the symptoms are generated by motor and not by secretory disturbances.

Certain people, usually with duodenal ulcer, secrete under basal conditions a larger volume of gastric juice of higher acidity than is ever attained in normal asymptomatic individuals. These excessive degrees of acidity may be correctly designated "hyperacidity" but this is a purely physiological (laboratory) diagnosis without definite clinical implications. Hyperacidity is only revealed when spontaneous (basal) gastric secretion is studied, since powerful stimuli such as histamine stimulate as high degrees of acidity in some normal people as are ever encountered in disease.

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The Effect of Pregnancy and of Antuitrin-S on Cinchophen Ulcers in Dogs*

By

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ELSEWHERE (1) we have noted that pregnancy has a beneficial effect on the symptoms of peptic ulcer in women. Experimentally, we have found that daily subcutaneous injections of Antuitrin-S (which

is obtained from the urine of pregnant women) has a beneficial effect on Mann-Williamson ulcers in dogs (2). We tried to determine whether the Mann-Williamson operation when performed on pregnant dogs would produce a lesser percentage of ulcers than when this operation was performed on normal non-pregnant

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animals. However, in our hands, all the pregnant animals aborted soon after this operation, which is, at best, rather a major one.

In searching for another type of experimental ulcer to test the supposed beneficial effect of pregnancy on ulcer, it occurred to us to use the one produced by cinchophen. In man, cinchophen in toxic doses produces liver damage and jaundice. In dogs, there is produced a toxic gastritis followed by multiple erosions, and then a few large penetrating ulcers on the lesser curvature. The animal invariably dies of hemorrhage or perforation unless the giving of the drug is stopped (3-8). Although the ulcer produced by cinchophen resembles human peptic ulcer, it is caused by a toxic gastritis, it is more frequent in the stomach than in the duodenum, and it heals as soon as the use of the drug is stopped.

METHOD

The cinchophen was made into a starch paste (20 gm. cinchophen, 40 gm. starch and 2000 cc. water) and a sufficient quantity of this mixture was given to each dog (mixed with food or via stomach tube once daily) to represent a dose of 100 mgm. per kilo of body weight. Thirty-four healthy dogs were used. Nineteen non-pregnant dogs served as controls and were given the above dose of cinchophen. Nine non-pregnant dogs were given subcutaneous injections of 1 to 5 cc. of Antuitrin-S daily in addition to the standard daily dose of cinchophen. The remaining 6 dogs were pregnant. They were given the above standard daily dose of cinchophen.

RESULTS

I. Ulcer incidence.

1. 19 control non-pregnant dogs fed with cinchophen.

8 died of ulcer, 7 of perforation (longest survival time 88 days, shortest 33 days, average 58 days).

11 were sacrificed after an average period of 85 days (longest 134 days, shortest 47 days). All of these had typical ulcers.

2. Nine non-pregnant dogs fed with cinchophen and injected daily with Antuitrin-S.

Five died of ulcer, two of perforation (longest survival time 90 days, shortest 30 days, average 67 days).

Four were sacrificed (one at 62 days, and 3 at 101 days). All of these dogs had typical ulcers.

3. Six pregnant dogs fed with cinchophen.

Four were sacrificed immediately after parturition. One was sacrificed 80 days after parturition and another died 95 days after parturition. All had typical ulcers.

The ulcers, usually located on the lesser curvature, were the typical large lesions, which have been described by others (3-8).

Microscopically, some of the control ulcers showed considerable fibroblastic proliferation but no epithelialization at the edges. Three of the pregnant dog ulcers and two of the Antuitrin-S dog ulcers showed, in addition to the fibroblastic proliferation, the beginning of epithelialization at the edges of the ulcers. We interpreted this as slight evidences of an attempt at healing.

II. In the experiments of Reid and Ivy (5) all the dogs fed on cinchophen died with gastro-duodenal ulcers within an average of 22.4 days (shortest survival time 7 days, longest 59 days). Our dogs lived 2 to 3 times longer. Ivy used Abbott's cinchophen. We used Merck's cinchophen.

Bringing this to Dr. Ivy's attention, and in an attempt to find the differences in the effectiveness of the two brands of cinchophen, Ivy (9) tested them for phenylquinoline. The older cinchophen supplied by Abbott and used by Reid and Ivy was light brown in color, gave a positive test for phenylquinoline and contained a second unknown impurity. The "newer" cinchophen, a white powder supplied by Abbott, like Merck's cinchophen also a white powder, gave a negative test.

With regards to Merck's cinchophen, Robertson (10) of Merck and Company states: "It is improbable that cinchophen (Merck) contains any uncombined phenylquinoline. The preparation conforms with the N. F. requirements which state that it should not contain less than 99.5% cinchophen and that the melting point shall be between 213 and 216 centigrade. Both of these requirements would insure the absence of any demonstrable quantities of combined phenylquinoline."

Therefore the admixture of a small quantity of phenylquinoline, or the unknown impurity, might be responsible for the increased effectiveness of the Reid and Ivy series compared to ours.

CONCLUSIONS

1. Pregnancy and injections of Antuitrin-S had only slight effect on cinchophen ulcers in dogs.

2. There was a definite difference in the rapidity with which ulcers were produced by two different commercial preparations of cinchophen. This may be due to a small admixture of phenylquinoline or the presence of the unknown impurity in one product and its absence in the other.

3. Mann-Williamson ulcers and cinchophen ulcers respond differently under treatment with Antuitrin-S.

Note: The authors are indebted to Dr. Donald Beaver, pathologist, for the gross and microscopic examinations of the specimens obtained at autopsy. Mr. Harold M. Padolsky assisted in this work.

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The Calcium Content of Gastric Juice*

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INTRODUCTION

RELATIVELY scant attention has been paid to the calcium content of gastric juice although the chemical composition of this fluid has been studied in detail. Rosemann (1) found that canine gastric juice, obtained after sham feeding, contained from 0.07 to 0.22 mg. per cent of calcium. Gamble and McIver (2) reported values ranging from 4.1 to 10.6 mg. per cent in the gastric juice of the cat (Heidenhain pouch secretion). Rudd (3) obtained values in man, varying between 4.1 to 8.6 mg. per cent. Rudd found that the calcium before histamine stimulation, in four cases, was between 3.08 and 6.30 mg. per cent, whereas after histamine, the figures ranged from 2.03 to 6.10 mg. per cent. Calcium was apparently present in smaller amounts in the very acid secretion following histamine, increasing in amount as the acidity fell. Klerks (4) found that the average calcium in the fasting gastric juice of 31 native patients (Java) was 4.4 mg. per cent, in 33 Chinese, 3.4 mg. per cent, and in 32 native students and servants, 3.6 mg. per cent.

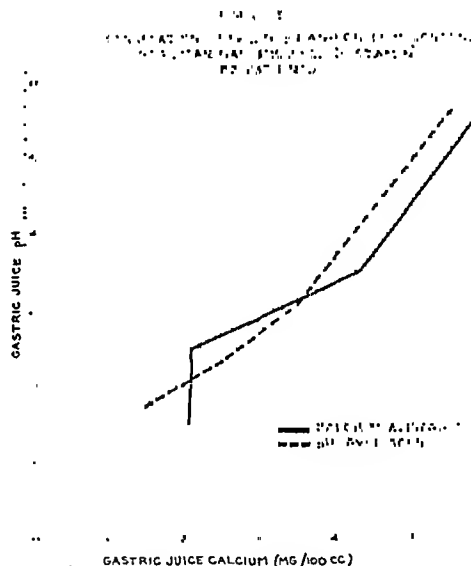
Our interest in this subject was stimulated, during the course of electrolyte balance studies, by the results in five patients in which calcium content of the gastric juice was approximately one-half the serum calcium (Table IV). This finding suggested the possibility that only the diffusible fraction appeared in the gastric contents. To investigate this problem further, the calcium content and hydrogen ion concentration of the gastric juice was determined in a series of 70 patients and five dogs.

METHODS

The gastric juice in five cases was obtained after Ewald test meal, and in sixty-five patients, after the injection of histamine (0.5 mg.). Many of the cases comprising this study were patients with healing or healed duodenal ulcer. Some of these patients were treated with calcium carbonate in amounts up to 35 grams daily. It is notable that the calcium in the gastric juice of these cases was no greater than in patients not receiving calcium carbonate.

The individual samples for each patient were thoroughly mixed and centrifuged at a rate of 1800 R.P.M. Ph determinations were made with the Beckman Ph meter which has a claimed accuracy of 0.05 Ph. The calcium was determined as follows: Two to four cc. quantities of the centrifuged gastric juice were pipetted into special 15 cc. centrifuge tubes, followed by the addition of 2 cc. of water and 1 cc. of saturated ammonium oxalate. The Ph was adjusted to approximately 4.60 using Brom cresol green as the indicator. After standing in the icebox overnight,

the samples were centrifuged and washed several times with dilute ammonia water. Two cc. of 5 per cent H_2SO_4 were then added, and the calcium was titrated with 0.1 N KmO_4 , freshly prepared, at 70° C. (5). All determinations were run in duplicate. Triple distilled water was used in preparing the solutions and washing the glassware. The serum calcium and phosphorus were determined in all patients at the time the gastric juice was obtained. The results were



uniformly within normal limits and, therefore, are not recorded on the charts.

RESULTS

The results are tabulated according to the Ph range of the gastric juice. In gastric juice with a Ph range of 1.49 to 1.91 (Table I) the calcium varied from 1.04 to 3.47 mg. per cent (average 2.06 mg. per cent). In gastric juice with a Ph range of 2.00 to 2.94 (Table II), the calcium varied from 0.85 to 3.75 mg. per cent (average 2.12 mg. per cent). In gastric juice with a Ph range of 3.05 to 8.38 (Table III), the calcium varied from 2.40 to 7.00 (average 4.54 mg. per cent). There seems to be a fairly close correlation between the Ph and the calcium content of gastric juice in that the higher calcium and Ph values usually were obtained in the same gastric juice. This correlation is further demonstrated by plotting the average values of calcium and Ph against each other ("lines of regression") as in Fig. 1.

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In five samples of fasting gastric juice, the Ph ranged from 1.61 to 2.19, while the calcium varied from 3.80 to 6.60 mg. per cent (average 4.61 mg. per cent) (Table IV). In five samples of gastric juice obtained after Ewald test meal, the Ph ranged from 1.70 to 4.49, while the calcium varied from 3.30 to 5.30 mg. per cent (average 4.18 mg. per cent) (Table IV).

TABLE I

*Calcium content of human gastric juice (histamine)
pH range between 1 and 2*

Patient	36 Patients	
	pH Gastric Juice	Ca mg./100 cc Gastric Juice
J. deV	1.49	1.40
G B	1.49	1.01
J P	1.60	1.40
A O	1.50	1.37
C M	1.50	1.75
B G	1.50	1.55
J K	1.50	1.07
J M	1.51	1.65
G H	1.51	2.00
E M	1.51	2.10
K M	1.52	1.11
O B	1.54	1.30
M O	1.55	1.75
L W	1.56	3.47
H S	1.59	1.50
V A	1.59	4.30
W N	1.59	1.70
J S	1.60	2.75
J S	1.60	2.30
J D	1.60	1.20
R W	1.60	1.85
J K	1.61	1.05
D O	1.61	2.10
J M	1.65	1.50
J I	1.66	2.50
R F	1.70	2.20
A O	1.70	2.30
R R	1.71	2.05
M P	1.71	1.55
D W.	1.73	2.57
C A	1.90	1.25
H S	1.89	1.70
J McC	1.89	1.65
F M	1.89	2.97
W K	1.90	1.50
M T	1.91	2.50

TABLE II

*Calcium content of human gastric juice (histamine)
pH range between 2 and 3*

Patient	17 Patients	
	pH Gastric Juice	Ca mg./100 cc Gastric Juice
B O	2.00	2.90
A Z	2.05	1.85
B K	2.08	1.72
W S	2.10	2.05
M T	2.11	2.45
H I	2.17	2.15
S Z	2.19	3.75
G M	2.21	2.35
W B	2.23	3.30
H B	2.25	2.50
A T	2.29	1.40
J M	2.30	1.70
P B	2.31	1.65
T W	2.35	1.51
D M	2.41	0.85
L Z	2.88	2.60
H G	2.94	3.29

These figures are in close agreement with the results reported by Klerks.

It will be noted that there is more calcium in fasting and Ewald meal gastric juice than in histamine stimulated secretion. Although the patients were instructed to avoid swallowing saliva, the possibility still remains that contamination with saliva accounted for the higher values. To rule out the possibility that calcium was added via the test meal, the following experiment was performed. Eight arrowroot cookies and 400 cc. of tap water (the usual meal) were thoroughly mixed, and two cc. aliquot samples were digested by boiling after the addition of concentrated nitric acid and ammonium persulfate. The samples were then diluted to 100 cc. volumes and analyzed for calcium in

TABLE III

*Calcium content of human gastric juice (histamine)
pH range above 3*

Patient	12 Patients	
	pH Gastric Juice	Ca mg./100 cc Gastric Juice
F A	3.05	4.00
A N	3.09	4.05
A R	3.36	3.00
H S	3.45	1.75
W G	3.99	4.70
R M	5.02	7.00
M T	5.19	5.65
J M	5.30	3.00
A W	7.02	2.40
E W	7.95	5.25
T B	8.05	5.90
I F	8.38	4.25

TABLE IV

Calcium content of human gastric juice

A Five Patients (fasting specimen)		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
O D	1.61	5.65
P C	1.70	5.30
H C	1.78	6.60
I S	2.00	3.80
D Mc	2.19	4.70
B Five Patients (Ewald test meal)		
Patient	pH Gastric Juice	Ca mg./100 cc Gastric Juice
M D	1.70	3.40
T S	1.81	3.30
C G	1.95	3.80
F K	1.91	5.30
F A	4.49	5.10

TABLE V

Calcium content of canine gastric juice

5 Dogs			
Dog	Type of Secretion	pH Gastric Juice	Ca mg./100 cc. Gastric Juice
A (pregnant)	Fasting	2.04	14.80
	Fasting	3.51	13.60
	Fasting	2.10	13.50
	Histamine (0.2 mg.)	2.09	11.07
A (5 days after delivery)	Fasting	2.50	12.80
	Fundic pouch	1.51	1.40
B	Fundic pouch	1.79	1.10
C	Fundic pouch	1.58	1.10
D	Fundic pouch	1.39	3.30

the manner previously outlined. Calcium was present in the Ewald test meal in negligible quantities.

Except in those patients with achlorhydria, it seems apparent that histamine stimulation yields a gastric juice of low calcium content, an observation made also by Rudd. The exact mechanism of this phenomenon is not yet clear, although it is conceivable that the greater volume of secretion obtained with histamine could, by dilution, account for the difference.

It is of interest to compare the results for human gastric juice with those obtained in the dog (Table V). The calcium in the fasting juice of dog A (pregnant) varied from 13.5 to 14.8 mg. per cent; following histamine stimulation (0.20 mg.), the value dropped to 11.07 mg. per cent, while after delivery, the fasting juice contained 12.8 mg. per cent of calcium. These results were considerably higher than those obtained in man. It should be noted, however, that contamination of the gastric juice with saliva occurred despite all attempts at its prevention. Accordingly, the calcium content of fundic pouch secretion was determined in four dogs. The values, 1.10, 1.10, 1.40 and 3.30 mg. per cent (Table V) approach more closely the results in man. It is impossible to state at this time whether or not the difference between dog A and dogs B, C, D and E, actually represents a significant variation in the gastric juice calcium of pregnant and non-pregnant dogs.

SUMMARY AND CONCLUSIONS

1. The calcium content of gastric juice with a Ph between 1.49 and 1.91 averaged 2.06 mg. per cent (36 patients). The calcium content of gastric juice with a Ph between 2 and 2.94 averaged 2.12 mg. per cent (17 patients). The calcium content of gastric juice with a Ph between 3.05 and 8.38 averaged 4.54 mg. per cent (12 patients).
2. Ewald test meal and fasting gastric juice contains more calcium than histamine stimulated secretion.
3. The gastric juice calcium in one pregnant dog was considerably higher than in man, while the calcium content of fundic pouch juice in four dogs was comparable to that in human gastric juice.
4. The calcium in human gastric juice, in these studies, was fairly well correlated with the Ph; usually the higher the Ph values, the higher was the amount of calcium.
5. The practical significance of these observations requires further study.

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The Effect Upon Gastric Secretion of Introducing Dilute Hydrochloric Acid Into the Duodenum

A Study of Normal Humans and Duodenal Ulcer Patients*

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THE therapeutics of duodenal ulcers has long been concerned with attempts to reduce the acidity of gastric contents. Usually prescribed for the ulcer patient are frequent feedings and alkaline substances which tend to neutralize acid. Another way to achieve the same end would be to lessen, in some manner, the stomach's rate of secretion. As yet no such procedure has become available for practical, clinical application. The experiments herewith reported constitute part of a search for just such a procedure.

The indications are that the stomach of an ulcer patient in the fasting state secretes considerably more gastric juice than is produced in a normal person. Winkelstein (1) has shown that the nocturnal gastric secretion of patients having duodenal ulcer is definitely higher in acid concentration and greater in volume than is that of normal subjects. Consideration of why this is so leads one into the physiology of gastric secretion in general, and, more particularly,

into what the factors are which terminate the usual post-cibal period of active, gastric secretion. Reports by Webster and Day (2), Gray and Ivy (3), Kosaka and Lim (4), Wilhelmj (5), Griffiths (6) and others show evidence of an active suppression of secretion in animals and in man following the post-cibal activity. Some (3) explain this as due to the action of a chalone called "Enterogastrone," formed in the duodenum; others (5) believe that it is the result of factors acting intragastrically. In any event, it appears likely that the HCl of gastric juice plays a role in effecting this suppression. Webster and Day (2), using dogs, showed that introduction of dilute HCl directly into the duodenum causes a significant suppression of gastric secretion. Griffiths (6) claims to have demonstrated a similar effect in humans.

Such observations allow one to postulate as a hypothesis that duodenal ulcers or the lack of healing may be partly the result of a deficiency state. It is possible that patients having duodenal ulcers may lack some important bit of the mechanism causing suppression of gastric secretion; their stomachs, therefore, con-

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tinue to secrete juice so that the total volume exceeds normal amounts. During the day, the excess acid may be masked by the diluting and neutralizing effects of frequent, small feedings. At night, however, feedings are omitted, and the acid gastric juice passes on into the duodenum relatively undiluted. As a test of this theory of deficiency, it is important to attempt to isolate and to define the missing factor. It might thus be possible to supply this factor to the patient having duodenal ulceration, cause his stomach to secrete in a more nearly normal fashion, and thereby eliminate a factor of chronic irritation of the ulcer, i.e., excessive quantities of acid.

We commenced these experiments with two main objectives:

(a) To determine the importance of HCl in the process of suppression of gastric secretion.

(b) To determine whether there is a difference between the gastric secretory curves of duodenal ulcer patients and those of normal subjects, after the introduction of HCl directly into the duodenum.

METHODS

Experiments on Humans Only

Subjects included eight healthy, male medical students, all free from signs and complaints of gastrointestinal disease, and three male patients having symptoms and X-ray evidence of duodenal ulcer in a state of acute or subacute activity.

Preliminary Conditions

Each subject started every experiment in the fasting condition, having had no food for twelve hours or more, and no water for at least two hours.

General Procedure

The subject swallowed a tube into his stomach, which was then emptied of its contents. Usually, immediately thereafter, the "basal secretion" was determined for a period of fifteen minutes. The lower end of the tube was then passed on into the duodenum, its position being checked by fluoroscopy. This was the procedure in each case, regardless of whether or not fluid was to be run into the duodenum, since it established a common mechanical background for each experiment. In every instance, when the lower end of the tube had served its purpose in the duodenum, it was pulled back into the stomach and was left there until the experiment ended.

The Stomach Tube Used

A single tube, Jutte duodenal type, was used in most of the experiments.

It was originally planned to use two tubes, one extending into the duodenum and the other ending in the stomach. Very soon we discovered the impracticality of this, since it permits the stomach to empty too rapidly and facilitates regurgitation of duodenal contents to dilute the gastric contents.

Method of Recovering Gastric Juice

In a few of the earlier trials, the stomach contents were obtained by aspirating periodically with a syringe. Later, constant suction was used, collections

being made at the end of every fifteen minutes. Most of the saliva was excluded by having the subject expectorate as soon as appreciable amounts had collected in his mouth.

Test Meal

The standard test meal used throughout was 300 cc. of a 2% aqueous solution of Liebig's extract, containing 15 mgms. per liter of phenol red (prepared according to Wilhelmj's directions) (8). Use of this preparation seemed justified on the basis of its being a physiological stimulant as well as its being the only test meal to account for the quantitative factors of dilution of the gastric contents.

Analysis of the Gastric Samples

The volume of each sample was recorded, but has not been charted unless it represents the approximate volume of gastric juice. (Some samples containing gastric juice and test meal were not analyzed for volume of gastric juice alone).

The total acidity of each sample was determined, corrections for dilution being made where necessary, according to directions by Wilhelmj. Titrations were done with 0.05 NaOH, using phenolphthalein as the indicator. Figures obtained by titration were then translated into terms of clinical units of HCl.

Variations of the Experiment

The one feature common to all of the experiments other than the "normal" or "control" runs was the introduction of HCl in some form into the duodenum. In some instances 0.4% HCl alone was used, in others gastric juice (which contains HCl) was used.

There are four main groups of the experiment.

(1) Normal Subject—0.4% HCl introduced into the duodenum.

(2) Normal Subject—Gastric juice introduced into the duodenum. (Gastric juice obtained from a person other than the subject himself). (Exogenous gastric juice).

(3) Normal Subject—Gastric juice introduced into the duodenum. (Gastric juice previously obtained from the subject himself). (Autogenous gastric juice).

(4) Duodenal Ulcer Patient—0.4% HCl introduced into the duodenum.

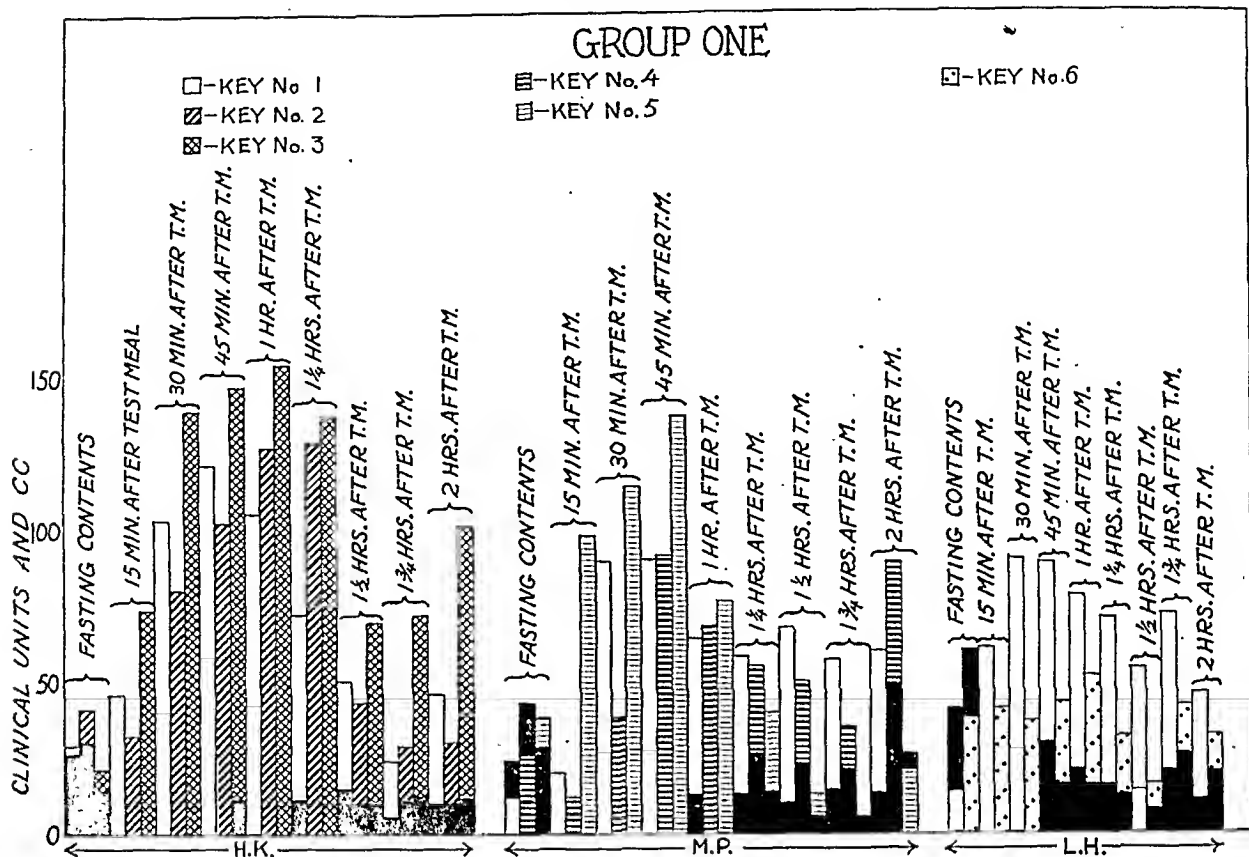
The relation of time of the intraduodenal infusion to giving of the test meal was altered from one experiment to the next. Thus, in one instance, half an hour elapsed between the intraduodenal infusion and giving the test meal. In another, the infusion was allowed to run through the entire length of the experiment. These variations are noted in the charts which follow.

RESULTS

Explanation of Graphs

All solid black columns represent the volume of a specimen expressed in cubic centimeters.

The blank and figured columns represent total acidity expressed in terms of clinical units of HCl. On all of the graphs, Key No. 1 designating the blank columns refers to results obtained when the subject was given the test meal alone; these columns, therefore, represent the "normal" or "control" figures for a basis of comparison.

**Group I**

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

(a) Using test meal alone. (Key No. 1)

(b) Using test meal accompanying and following the introduction of 0.4% HCl into the duodenum. (Keys No. 2, 3, 4, 5 and 6)

H.K.

Key No. 2. These columns represent figures obtained when the test meal was given immediately following completion of 1/2 hour drip of 0.4% HCl (Vol. 125 cc.) into the duodenum.

Key No. 3. These columns represent figures obtained when the test meal was given 1/2 hour after completion of an intraduodenal infusion. (120 cc. of 0.4% HCl were dripped into the duodenum over a period of 25 minutes).

M.P.

Key No. 4. These columns represent figures obtained when a drip of 0.4% HCl was continued throughout the period of experiment. (Two tubes were used). Rate of flow was 30 drops per minute.

M.P.

Key No. 5. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (140 cc. of 0.4% HCl were dripped into the duodenum over a period of 30 minutes).

L.H.

Key No. 6. These columns represent the figures obtained when the test meal was given 5 minutes after completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were run into the duodenum over a period of 5 minutes).

Group II

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

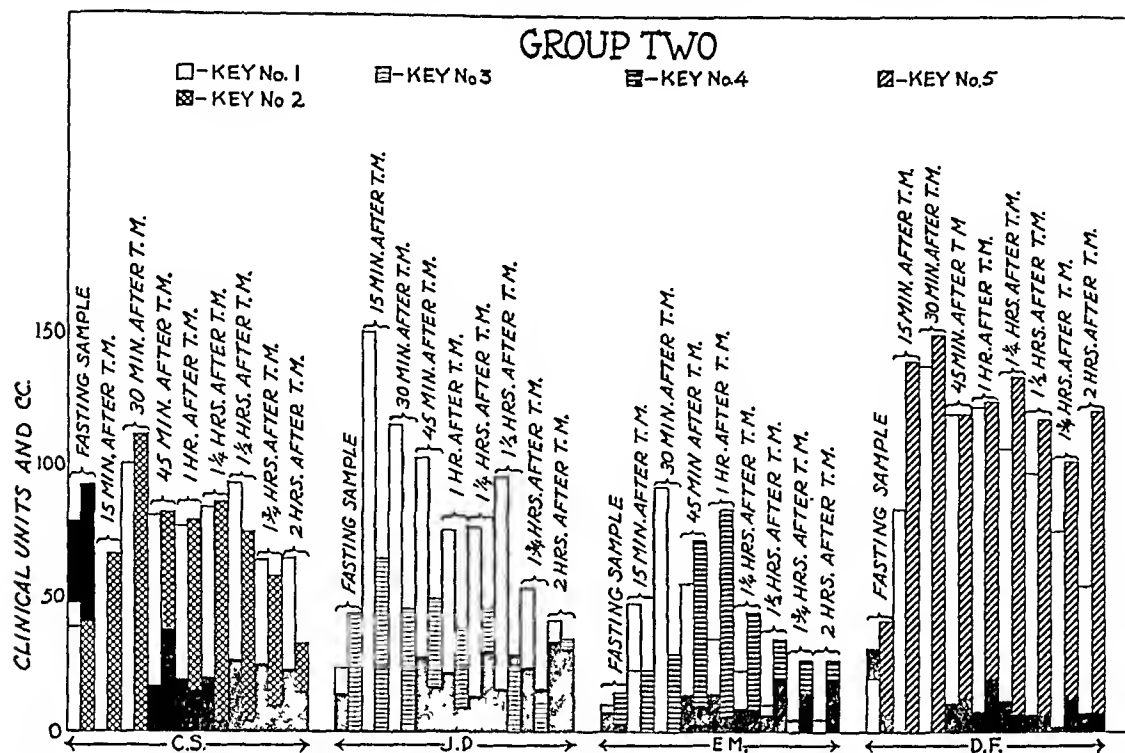
(a) Using the test meal alone. (Key No. 1)

(b) Using the test meal after the introduction of gastric juice into the duodenum. (Gastric juice used for the intraduodenal infusion was exogenous, i.e., was obtained from a person other than the subject). (Keys No. 2, 3, 4 and 5)

Explanation of Graph

In all of the experiments represented by this graph, except for control runs, the test meal was given immediately following completion of an intraduodenal infusion of gastric juice. The keys indicate the source of this gastric juice and the time involved in giving the infusion.

Gastric juice used for the infusion was obtained from a normal subject by using the Liebig extract test meal as a stimulant. Collections were made as usual every 15 minutes. The first four samples were pooled to form the substance of the infusion. Volume and total acidity of the pooled gastric juice were determined in each instance.



The two subjects required for each of these experiments were both present at each trial run; thus there was a minimal delay between obtaining the gastric juice from one subject and infusing it into the duodenum of the other.

C.S.

Key No. 2. 55 cc. of gastric juice obtained from the subject J.D. were infused by gravity over a period of 5 minutes.

J.D.

Key No. 3. 50 cc. of gastric juice obtained from the subject C.S. were infused by gravity over a period of 15 minutes.

E.M.

Key No. 4. 33 cc. of gastric juice obtained from the subject D.F. were infused by gravity over a period of 10 minutes.

D.F.

Key No. 5. 28 cc. of gastric juice obtained from the subject E.M. were infused by gravity over a period of 15 minutes.

Group III

Gastric Secretory Response in Normal Human Beings to Liebig Extract Test Meal:

(a) Using the test meal alone. (Key No. 1)

(b) Using the test meal after the introduction of autogenous gastric juice, i.e., previously obtained from the same subject, into his duodenum. (Keys No. 2, 3 and 4)

These experiments were performed with the idea in mind that some factor or factors other than the HCl

of gastric juice might be responsible for the apparent inhibition of gastric secretion resulting from the interaction of gastric juice and duodenal mucosa; furthermore, that these factors might be specific, i.e., a subject showing no inhibition when gastric juice obtained from another person is introduced into his duodenum might show this inhibition when his own gastric juice is so employed.

A "normal" or "control" experiment was run on the subject. The first four specimens collected after giving the test meal were pooled, and determinations of volume and total acidity were made. This pooled gastric juice was then placed in an ice box for use as the substance of an intraduodenal infusion on the following day. Specimens were not used when more than 24 hours old.

Explanation of Graph

In each of the experiments of this group other than the normal runs the test meal was given immediately following completion of the intraduodenal infusion. The keys thus refer to the experiments and give the volume and time involved in giving the infusion.

C.S.

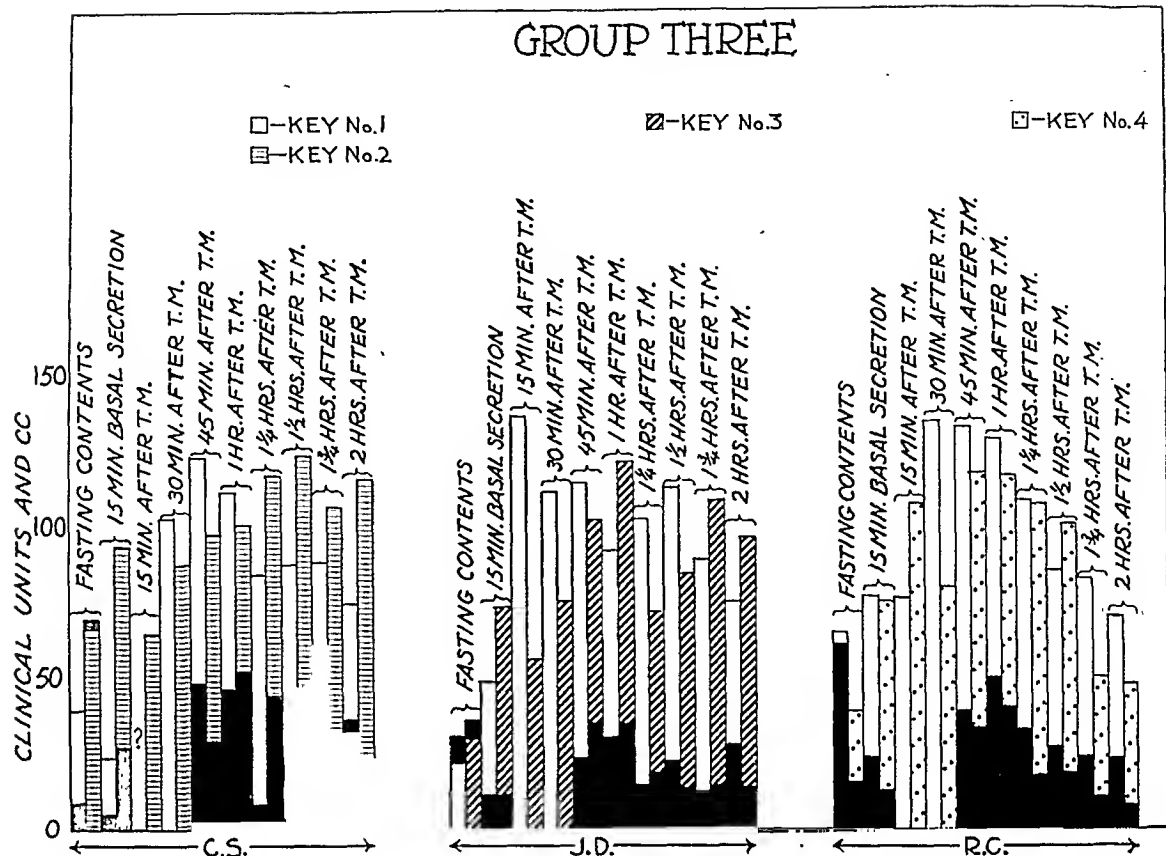
Key No. 2. 90 cc. of gastric juice were infused by gravity over a period of 10 minutes.

J.D.

Key No. 3. 83 cc. of gastric juice were infused by gravity over a period of 10 minutes.

R.C.

Key No. 4. 139 cc. of gastric juice were infused by gravity over a period of 10 minutes.



Group IV

Gastric Secretory Response in Duodenal Ulcer Patients to Liebig Extract Test Meal:

- (a) Using the test meal alone. (Key No. 1)
 (b) Using the test meal after the introduction of 0.4% HCl into the duodenum. (Keys No. 2, 3 and 4)

Explanation of Graph

J.M.

Key No. 2. These columns represent figures obtained when 0.4% HCl was allowed to drip into the duodenum throughout the entire experiment. (Two tubes were used. The rate of flow was about 30 drops per minute).

S.F.

Key No. 3. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were dripped into the duodenum over a 15 minute interval).

E.C.

Key No. 4. These columns represent figures obtained when the test meal was given immediately following completion of an intraduodenal infusion. (125 cc. of 0.4% HCl were run into the duodenum over an interval of 3 minutes).

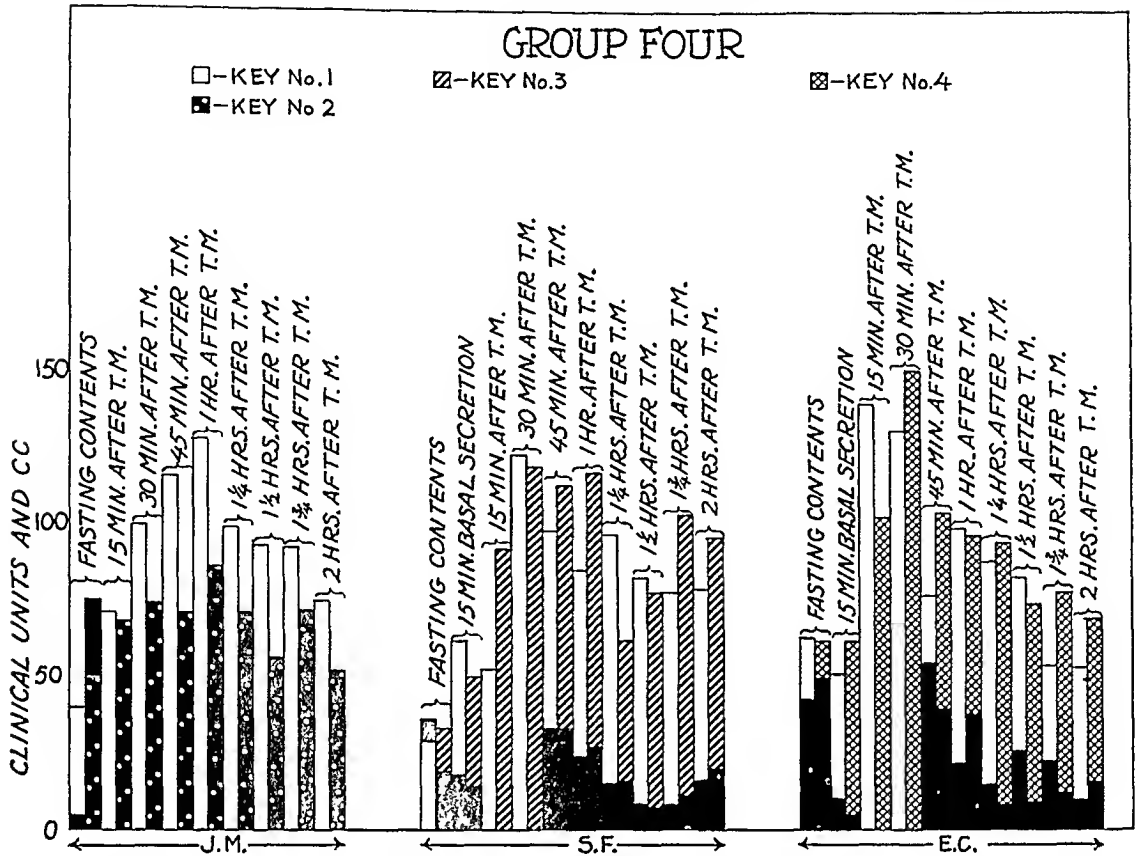
DISCUSSION

Considering our results as a whole, there is no consistent trend indicating any momentous suppression of gastric secretion under the conditions of our experi-

ments; individual instances seem to indicate at least a temporary suppression, but repetition of the same or of a related experiment on the same subject failed to confirm such a suppression. Furthermore, there are no indications that the gastric secretory response of duodenal ulcer patients is significantly different from that of normal subjects, following an intraduodenal infusion of 0.4% HCl.

This does not necessarily disprove the work of the experimenters mentioned in the introduction, since the conditions of the experiments were different. Webster and Day worked with dogs, and the suppression which they obtained by introducing HCl directly into the duodenum was during the intestinal phase of gastric secretion. Griffiths worked with humans; but he used an alcohol test meal, and a mixture of NaCl, HCl and glucose for the intraduodenal infusion. We attempted to maintain the conditions of our experiments on as nearly a physiological basis as possible. For this reason, we used a meat extract test meal and set the concentration of HCl at 0.4%. When it had become apparent that an intraduodenal infusion of 0.4% HCl would not suppress gastric secretion, we replaced the HCl with normal human gastric juice thinking that other factors plus the HCl might effect gastric suppression. However, this is apparently not so.

It is possible, of course, that the strength of the stimulus is so great that it masks the evidence of a suppression which actually does exist. Thus it may be that we were mistaken in trying to cope with the



gastric phase of secretion. The next logical step is to see whether HCl in the duodenum will suppress or abolish the intestinal phase of gastric secretion. Implications in the literature are not very definite concerning details of the intestinal phase of gastric secretion in humans. Possibly it is a prolonged intestinal phase in duodenal ulcer patients which is responsible for the secretion of relatively large quantities of gastric juice. Any practical means of stopping the intestinal phase of secretion would therefore be a valuable addition to our therapeutic armamentarium.

It appears likely that if suppression of gastric acidity is to be attained, it will be done by reducing the volume of acid secreted and not by reducing the concentration of the acid as it is secreted by the parietal cells.

CONCLUSIONS

HCl in 0.4% solution or in gastric juice, when introduced into the duodenum of normal subjects, had no

constant, significant effect on gastric secretory curve.

HCl in 0.4% solution, when introduced into the duodenum of duodenal ulcer patients, had no constant, significant effect on gastric secretory curve.

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Lymphogranuloma Venereum Surgical Aspects

By

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THE very serious surgical problems presented by lymphogranuloma venereum have not received adequate consideration up to the present. The likely reason is that this condition is classifiable among the venereal diseases and thus escapes a thorough evaluation from the surgical point of view. The object of this report is to present the various means of surgical therapy employed thus far; their advantages and shortcomings.

In its various clinical manifestations, lymphogranuloma venereum presents essentially inflammatory lesions of the different organs affected. The disease picture is very similar to other inflammatory lesions appearing in acute, sub-acute or chronic stages. From the point of view of surgical therapy, the laws governing surgical intervention apply, for the most part, in this disease as they do in other inflammatory diseases. An important point of difference between lymphogranuloma and bacterial pyogenic lesions is the fact that this disease is the result of an infection by a filtrable virus. Bacteriologic cultures of pus removed from diseased tissue are sterile. It differs also in the fact that although the anatomic structures involved are those in the pelvis primarily the disease process itself is nevertheless systemic (1, 2). The extent of the inflammatory lesion will depend upon the amount of destruction that will take place because of the activity of the virus, both locally and systemically. With this in mind, a direct approach toward local therapy alone, would appear inadequate to combat this disease effectively. On the other hand, a combined systemic and local therapy seems more rational.

The natural course of the disease process in its primary lesions, inguinal, rectal and genital manifestations, as compared with cases treated, will serve to evaluate the surgical procedures alone as they have been employed thus far.

THE PRIMARY LESION

The acute primary lesions on the genitalia or elsewhere in the body, such as occur in accidental inoculation or by perversion, require no surgical therapy. They are generally evanescent in character and regress spontaneously within a period of two weeks.

THE LOCAL ADENOPATHIES

Inguinal or femoral glandular enlargement will begin from one to three weeks after the onset of the initial lesion. The progress of the lesion is rapid and reaches its height in about three weeks. By that time, that is, six weeks after contact, the glands begin to subside or promptly go on to suppuration. Spontaneous subsidence occurs in about 30% of the cases in a large series (3). The remainder, if untreated, will ultimately break through the skin and form one or more

spontaneous sinuses, which will drain for a variable length of time.

The choice of surgical procedures in these conditions consists of:

1. Incision and drainage.
2. Excision of all diseased tissue, with or without drainage.

3. Bilateral block dissection of the inguinal nodes.

Where incision and drainage were employed, the time of disability was approximately two weeks in the hospital, and from one to seven months for dressings, before a patient was discharged (4).

Block dissection of the lymph nodes yielded better results from the point of view of time. Healing took place within a period of two months.

Since the iliac and other pelvic lymph nodes are simultaneously involved in about one-third of the cases observed, the probability of the removal of all of the diseased tissue is very remote. The fact that elephantiasis of the genitalia may take place after a complete extirpation of the inguinal nodes, also militates against the use of this procedure. It is interesting to note that no drainage was used in two cases and that healing by primary union took place in spite of the presence of frank pus. Complete closure was used, in view of the fact that the pus present was sterile to the usual culture.

The pelvic lymphadenopathy does not create any surgical problems. No case of suppuration breaking through the peritoneum has thus far been reported. An iliac abscess which yielded 300 cc. of pus was observed by the author. The abscess broke through the skin spontaneously above Poupart's ligament and then subsided. Pelvic exudates have been observed but none drained. Abdominal pain due to a mesenteric adenitis necessitating laparotomy, has been reported (2). Without any treatment or with radical surgical therapy, most of the cases seen healed completely at the end of seven months.

With the introduction of a combined systemic and local treatment, the results have proved more satisfactory. In 176 cases only 40% came to suppuration and among the latter, aspiration of the local pus collection in addition to the use of intravenous Frei material sufficed for healing in an average period of six weeks. Among these cases there was no necessity to perform any operative procedure besides aspiration. Sinus formation at the point of puncture took place in few instances. Repeated aspiration was necessary in a minority of cases. Where a sinus formed, the administration of the Frei antigen hastened a spontaneous closure without resort to any other surgical means. In a number of cases where fluctuation was already present, the intravenous therapy was sufficient to cause a complete absorption of the local suppuration, and regression of the entire disease process. The systemic therapy in the inguinal variety of this disease is very

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encouraging and points toward conservative rather than radical procedures as adjuvants in attempts at cure (4). Surgical treatment of the inguinal bubo was contraindicated by John Hunter, as long ago as 1786 (5). He advised his patients to avoid the surgeon as much as possible during the affliction and take a rest cure instead. For the most part his advice still holds true.

RECTAL LESIONS

The natural course of the rectal lesions is one that leads to chronicity. The lesions present range in order of severity from:

1. Fistulas in Ano.
2. Perianal-Condylomas.
3. Acute and chronic proctitis due to pedercasty or secondary to previous inguinal and pelvic adenitis.
4. Ulcerative procto-sigmoiditis.
5. Rectovaginal fistulas.
6. Rectal stricture, which may be tubular or diaphragmatic in type.

Although the rectal lesions have been seen to develop as early as six weeks after exposure (6), the usual duration of the rectal lesion is at least two years before it is seen. Thus the examiner is most often faced with a chronic inflammatory lesion.

The procedures suggested for radical cure up to the present, have been as follows:

1. Complete resection—Lahey method.
2. Abdominoperineal resection with preservation of the sphincter ani.
3. Perineal approach with sacral anus.
4. Mobilization of the rectum with excision of perirectal scar tissue.
5. Permanent colostomy with subsequent dilatation of the stricture.
6. Temporary colostomy.
7. Dilatation, with or without anesthesia.
8. Incision or excision of fistulous tracts.

The follow-up of a large series of cases by Anschuets, Peterson (7) and Frei (8), has proved the operative mortality in the complete operation, in many stages or in one stage so disastrous, that the further use of the procedure is to be discouraged.

The causes of failure are evident when the procedure is attempted. The mobilization of the diseased rectum is extremely difficult. The normal anatomic planes of cleavage are entirely obliterated and replaced by inflammatory scar tissue in which active inflammatory elements may be demonstrated as long as twelve years after the onset of the disease (4). The mesosigmoid likewise become shortened by contiguity to the inflammatory lesion below. This most often prevents an adequate mobilization for a successful anastomosis. Preservation of the sphincter is a practical impossibility in most cases, because the perianal tissue is most often itself involved. Over 75% of the rectal lesions reported are tubular in type. In the remaining group the lesions are diaphragmatic in nature. In any event, the portion of the rectum distal to the lesion is most often involved and cannot be used in the repair.

Another most important cause of failure and high mortality is the fact that as long as there remains any evidence of activity of the disease, one must assume that a phlegmonous type of inflammation is still present in the endopelvic fascia. Attempts at dissection in such tissue is analogous to incision of a phlegmon elsewhere and carries with it the risk of a

lymphatic spread of the disease. Among all authors such radical procedures are cautioned against.

Radice classified (9) his rectal lesions as freely movable or fixed in the pelvis. He suggested that the tubular stricture of the fixed type be treated by colostomy, while the diaphragmatic freely movable, by dilatation. This procedure is reasonable. One report reveals 31 colostomies performed among 160 cases, and in only one case was it possible to close the colostomy subsequently (10). The question of using colostomy as a permanent or temporary procedure necessarily will depend upon the indications present.

Dilatation alone is contraindicated in the presence of active proctitis or periproctitis and is associated with severe general reactions. Because of the severity of the systemic symptoms, this procedure has been abandoned at the Presbyterian Hospital (1). Dilatation may be used with impunity and good effect in cases of chronic stricture, where the active disease has subsided and where the stricture actually represents the healed stage of this disease. In such cases proctoscopy will reveal a smooth mucous membrane, sometimes atrophic and in many cases showing stratified squamous epithelium which grew upward from the anal margin to replace the columnar epithelium which sloughed in the process of repair. Mathewson (11) is particularly impressed with the efficacy of dilatation alone.

Colostomy however has to be resorted to as an emergency procedure at times. Gutman (1) mentions three cases of deaths from peritonitis due to perforation after obstruction due to lymphogranuloma of the rectum. Although such cases are fortunately rare, they must be kept in mind when they do arise.

Temporary colostomy with isolation of the distal segment for rest and irrigation may serve to prepare the patient for an eventual healing of his disease.

The operation of "Evacuation of the Perirectal Space and Retroproctitic Mobilization of the Stricture" reported by Gomez (12), has failed to yield the results claimed for it. It has thus far resulted only in stirring up any latent infection in the endopelvic fascia and has always produced recurrences which were worse than the original condition for which the operative procedure was undertaken. In cases of healed strictures of the "ring" type, this procedure becomes unnecessary, since dilatation alone is sufficient. In tubular stricture where latent inflammatory foci are always present, the procedure is both dangerous and entirely unsatisfactory, since no mobilization is possible. All of the pelvic structures are agglutinated into a compact mass.

The suggestion of Lockhart-Mummery (13) may well be followed as a general principle in the treatment of inflammatory rectal strictures.

"To ascertain the type and extent of the stricture, it is advisable to examine even with partial dilatation, so that the upper limits can be explored and the condition of the proximal bowel immediately above verified. Sigmoidoscopy may thus be performed under anesthesia if necessary. This should be done with great care and splitting of the rectal wall when inflammation is present, should be avoided. In suitable cases the stricture is dilated and treated by continual cleansing. Results of internal proctotomy with subsc-

quent dilatation are excellent and permanent, if the patient will endure the inconvenience of dilating long enough to counteract the contraction of scar tissue."

In case of partial obstruction, colostomy may be optional. However, colostomy may be delayed or possibly entirely avoided by the use of the intestinal tube for abdominal decompression, described by Abbott and Johnston (14). After the distension is relieved, sufficient time may be taken for a thorough investigation of the case in point, and the most suitable course followed.

Colostomy as a general rule should be seriously considered in cases of fulminating lesions which do not react favorably to palliative measures or attempts at immunization with Frei antigen. Cleansing of the distal loop and rest, have proved very useful and permitted a late closure in some cases. This is illustrated in the case reported here.

Treatment with Frei antigen intravenously alone, i.e., 0.3 cc. of antigen every other day, has proved disappointing in these rectal lesions from the point of view of complete resolution. The treatment which takes many months to show appreciable changes, is, nevertheless, definitely of benefit to the patient. A noticeable symptomatic improvement is promptly obtained. The bloody purulent discharge becomes less and any painful defecation markedly improved. The constitutional symptoms are promptly relieved. The patients gain weight and lose their sense of weakness. Their general sense of well being is restored. After months of treatment the local lesions show a tendency to healing. The progressive nature of the disease is altered to a state of a chronic, slowly healing lesion. The late lesions generally observed are those which have gone on to spontaneous healing and consequent stricture formation of those in the process of fibrosis.

Incision and drainage or excision of fistulas leave chronic sinuses and lead eventually to recurrences. Radical surgical procedures among this group are exceedingly unsatisfactory.

Palliative methods such as rest in bed, low residue, high vitamin diet, retention enemata of olive oil or cottonseed oil and rectal irrigations with tannic acid solutions, or quinine bisulphate 1:4000, have been used with benefit to the patient.

From the foregoing one may reasonably conclude that radical surgical procedures alone or palliative methods alone are inadequate for either palliation or cure. A rational combination of both palliative procedures and the more conservative surgical methods seem the most advisable course to take at present.

The earliest treatment of rectal stricture by four incisions of circular bands with a bistoury and subsequent dilatation, is recorded by Dupuytren in 1854. Colostomy was successfully performed in 1710 by Littre' (15). Thus the treatment advocated at present is relatively old and simpler in comparison with the more radical procedure envisaged by Von Volkmann in 1887. However, reliance on less radical means seems more advisable until the systemic disease itself is controlled. Then, and then only will the mortality due to the radical removal be reduced. And it is possible to conjecture that the radical procedure may then become unnecessary.

GENITAL LESIONS

The genital lesions observed may be enumerated as follows:

1. Periurethral ulcerations and edema obstructing the urinary flow with resulting urinary retention.
2. Penile lesions—bubonuli and paraphymosis.
3. Elephantastic lesions of the vulva with overhanging pendulous masses.

The surgical problems presented by the chronic genital lesions are first those related to the establishing of a correct diagnosis by biopsy. This is a necessary procedure to exclude other known pathologic lesions such as tuberculosis, syphilis, and carcinoma. The pathologic lesion on the genitalia although not pathognomonic, is nevertheless suggestive of the disease in question and is thus most important. The main problem of surgical therapy is associated with the relief of stenosing lesions of the genital orifices—i.e.: the urethra, and vagina. Among these lesions it was not found necessary to resort to cystotomy in any case reported thus far. The more conservative methods sufficed to cause the more acute edematous lesions to subside. Among this group as in the rectal group of lesions it is important not to attempt repair of any fibrotic distorted parts until the disease process has completely subsided. Excision of pendulous condylomas may then be done and satisfactory healing may be expected.

In view of the above discussion, the treatment of two cases of rectal lymphogranuloma observed at the Gouverneur Hospital is presented.

CASE REPORTS

Case 1—History: P. C., a 56 year old white male, was admitted to the surgical service of Dr. Frank J. McGowan on November 6, 1937.

The patient had vomited repeatedly for thirty-six hours and suffered moderate abdominal distention. Three hours before admission he became extremely weak, perspired profusely and suffered a general collapse.

Eighteen years before the present admission, i.e.: in 1919, a cecostomy was performed because of a "severe inflammation of the rectum." After local treatment of the rectal lesion, the cecostomy was finally closed ten years later, i.e.: 1929. Between 1929 and 1937 the patient had suffered repeated attacks of subacute intestinal obstruction. The attacks were ascribed to incarceration of a right inguinal hernia which was, however, always reducible.

Examination: The patient appeared acutely ill and in shock. The abdomen was moderately distended. The inguinal canals were both clear. No masses were felt in the abdomen.

On rectal examination a definite stenosis was encountered at 5 cms. from the anal margin. The rectal wall was, however, fully movable in the endopelvic fascia. The stricture was annular and barely admitted the tip of the index finger. Proctoscopy confirmed the digital finding. The mucosa was pale and shiny. In the region of the stricture the mucous membrane had a cobble stone appearance, bled easily. Islands of squamous epithelium were seen running along the rectal wall with scarring suggestive of healing of a previously acute lesion.

Laboratory findings: The Wassermann reaction was three plus. The Frei test was markedly positive. A biopsy specimen from the region of the stricture revealed rectal tissue showing chronic inflammation. There was no evidence of any specific lesion.

Course: In view of the signs and symptoms of subacute intestinal obstruction, a temporary sigmoidostomy was

performed by Dr. Francis M. Conway. When the abdominal cavity was explored, the constriction could be felt in the rectum below. The entire colon above the line of stenosis appeared free and uninvolved. The colostomy functioned well and the distal loop was cleansed with saline. Three weeks after colostomy the patient was taken to the operating room and the stricture dilated, with bougies. Very little trauma was caused by this procedure. The mucous membrane above the stricture was found, by sigmoidoscopy, to be entirely clear and uninvolved.

The patient was observed for two months, during which time the colostomy was permitted to close. Rectal dilatation with a large bougie was performed every other day. There was no evidence of recurrence of the stricture. The patient was asymptomatic when discharged, three months after admission to the hospital.

Case 2—History: E. G., a 40 year old colored woman, was admitted to the surgical service of Dr. R. Franklin Carter on March 20, 1936.

She complained of difficulty in passing her bowel movements, for two years. Her symptoms became worse six months before admission. She had passed blood streaked fecal material on different occasions. She had had no previous operations. She had a number of still births but no live children. The patient was known to have had syphilis for three years, for which she had received two intravenous injections of arsphenamine.

Examination: The patient was well developed and well nourished. Her pupils were unequal and irregular. Both ankle jerks and knee jerks were sluggish. The abdomen was soft, no masses were felt.

Rectal examination revealed a narrowing at 3 cms. from the anal margin, which did not admit the tip of the index finger. Proctoscopy revealed a stricture of the rectum at 3 cms. The mucosa was pale and smooth. There was no evidence of any acute lesion.

Course: A cecostomy was performed. Three weeks later the stricture was dilated under spinal anesthesia. This procedure revealed a diaphragmatic stricture which was dilated with little trauma. The patient made an uneventful recovery and was discharged one month after admission.

Laboratory findings: The Frei test was positive. The Wassermann test was negative. The spinal fluid Wassermann was negative.

A biopsy of the rectal tissue showed chronic non-specific inflammation.

Readmission: July 25, 1936. The patient returned to the hospital because of a persistent sinus at the site of the cecostomy. During this three months interval, she had normal, regular bowel movement and no complaints except the presence of a purulent discharge from her abdominal sinus.

The cecostomy sinus was closed. When the patient was examined, the rectum was found to be narrowed, beginning at the internal sphincter. The rectum felt thick and indu-

rated. The constricting band was again thoroughly dilated. She was discharged 16 days after admission.

Readmission: September 10, 1936. The patient was readmitted because of an attack of La Grippe.

Rectal examination showed a well dilated rectum. There was no evidence of stricture.

She had one bowel movement daily without difficulty. The cecostomy wound was completely healed.

DISCUSSION

Two cases of rectal lymphogranuloma are presented. One in a white male and the other a colored female. In both cases the lesions seen upon examination represented diaphragmatic narrowing of the rectum as healed stage of a preexisting acute proctitis. Both of these cases were amenable to conservative surgical therapy.

CONCLUSIONS

1. Lymphogranuloma venereum is a systemic disease, in spite of the fact that its external manifestations are mainly lesions in the pelvic region.
2. The disease lymphogranuloma venereum in all of its manifestations presents essentially lesions which are due to the results of inflammation in any of its stages.
3. These lesions range from the acute exudative processes to the final chronic proliferative or fibrotic conditions of the various structures affected.
4. Surgical treatment alone, or palliative therapy alone have thus far proved inadequate for the complete cure of this disease.
5. Surgical indications in lymphogranuloma are identical with those in any other inflammatory conditions.
6. Surgical intervention is found most useful and least harmful when both systemic and local symptoms and signs have subsided.
7. The most useful procedures in all of the lesions seen in lymphogranuloma are the conservative ones, in combination with local palliative, and systemic Frei antigen intravenously.
8. Thus, for the inguinal adenopathy, aspiration and Frei antigen are suggested.
9. For the rectal lesions temporary or permanent colostomy as indicated; dilatation where possible in combination with local palliative and systemic Frei antigen intravenously are advised.
10. For the chronic genital lesions, conservative surgical therapy after complete subsidence of the inflammatory lesions is deemed most satisfactory.

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Intravenous Modification of the Hippuric Acid Test for Liver Function*

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THE hippuric acid test for liver function, which the author introduced in 1933 (1), has technical advantages as well as disadvantages. Its simplicity requires no comments; its inexpensiveness makes it widely available; and the fact that it requires no intravenous injections is a significant advantage when veins need to be conserved, or are difficult to inject. The chief disadvantage is the occasional vomiting which may occur after the oral administration of sodium benzoate. At times too, it is burdensome to collect four hourly specimens of urine. To meet these difficulties the author with Ottenstein and Weltehek (2) presented an intravenous modification.

Recently Lipschutz (3), unaware that such a test had been presented, also published an intravenous method which is very similar in some respects to our modification. Thus, Lipschutz injects 2 gm. of sodium benzoate dissolved in 20 cc. of water, while we give 1.77 gm. in the same amount of water. This little difference is obviously of no importance. His test, however, differs distinctly in one particular, and this leads to an erroneous interpretation. He collects the urine for two hours, determines the amount of hippuric acid excreted during this period, and from this calculates the per cent of the injected benzoic acid which is excreted. Lipschutz thus introduces a concept which is at variance with the original idea of the test. In my test the per cent of administered benzoic acid which is excreted as hippuric acid does not enter into consideration. As a matter of fact, approximately 75 per cent of the benzoic acid given to a normal adult is excreted and 25 per cent is lost, presumably burned in the body. There is no evidence that the amount of benzoic acid which fails to be excreted is related to hepatic dysfunction. The fundamental idea on which my test is based is the measurement of the rate with which hippuric acid is synthesized. In my comprehensive study of the conjugation of benzoic acid in man (4), I established the fact that irrespective of the dose of sodium benzoate administered, the maximum amount of hippuric acid formed per hour is practically constant. This is illustrated in Chart 1. The most rational explanation is that the amount of glycine which the liver can synthesize and conjugate with benzoic acid is limited, and that the hippuric acid output therefore measures the maximum functional capacity of the liver. If hepatic damage occurs, the hourly output is definitely diminished as has been repeatedly confirmed clinically. It is therefore essential that in both the oral and in the intravenous test an amount of benzoic acid be given in excess of the liver's capacity to conjugate within a fixed period of time. This can be readily illustrated by the data of Table I. When a normal subject is given 1.77 gm. of sodium benzoate intravenously, he will excrete 0.7 to 0.95 gm.

of benzoic acid as hippuric acid during the first hour and only from 0.13 to 0.36 gm. during the second hour. Obviously only the first hour measures the maximum functional capacity of the liver to synthesize hippuric acid. From these results, 0.7 gm. benzoic acid has been accepted as the minimal normal hourly excretion. A patient who excretes 0.5 gm. of benzoic acid during the first hour after receiving sodium benzoate intravenously would be reported as having a functional efficiency of 70 per cent. Such a patient, however, will in 2 hours excrete approximately 1 gm. of benzoic acid, and on the basis of Lipschutz's interpretation would be considered normal because he is excreting as much

TABLE I

The excretion of hippuric acid following the intravenous injection of sodium benzoate

Subject	Weight	Hippuric acid (expressed as benzoic acid) excreted	
		1st Hour	2nd Hour
	Kg.	Gm.	Gm.
1	62	0.71	0.31
		0.73	0.36
2	70	0.95	0.16
		0.91	
3	73	0.84	0.13
		0.92	
4	84	0.76	0.30
5	65	0.82	
6	73	0.79	
7	75	0.82	
8	78	0.84	0.34
9	70	0.90	0.28

1.77 gm. of sodium benzoate (equivalent to 1.5 gm. benzoic acid) dissolved in 20 cc. of distilled water was injected intravenously.

benzoic acid in 2 hours as subject No. 1 of Table I, who, nevertheless, has a normal functional liver.

The procedure for the intravenous hippuric acid test as it is employed in my laboratory and in various hospitals and clinics is as follows: The test is done preferably in the morning after the patient has had a light breakfast. A solution containing 1.77 gm. of sodium benzoate (equivalent to 1.5 gm. of benzoic acid) in 20 cc. of distilled water is given intravenously. At least 5 minutes should be taken for the injection. The patient is instructed to void before the test, and to collect the urine exactly one hour after the completion of the injection.

The urine is carefully measured and solid ammonium sulfate added in the proportion of 5 gm. for every 10 cc. of urine. When the salt is dissolved the urine is

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either filtered or centrifuged. Enough concentrated hydrochloric acid is added to make the urine distinctly acid to Congo red or to thymol blue. Usually 1 cc. of the acid is sufficient, but it is absolutely necessary to check with an indicator paper. An excess of acid is permissible. The solution is vigorously stirred until the precipitation of hippuric acid is complete. After

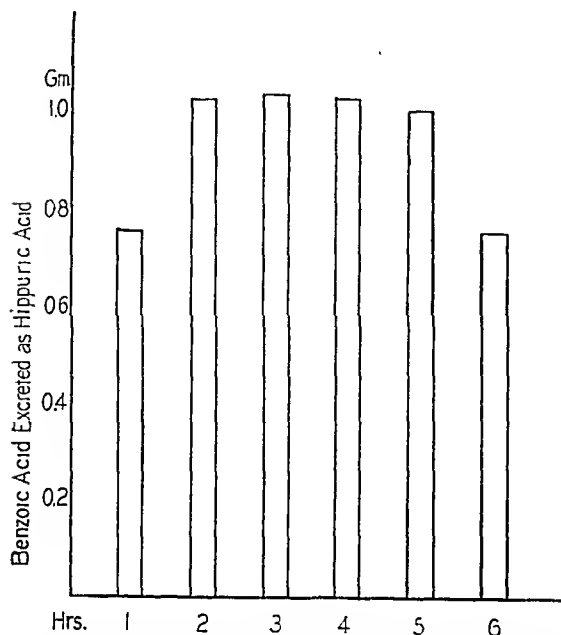


Chart 1. The constancy of the rate with which hippuric acid is synthesized. The subject, an adult male weighing 77.5 kg., was given 9.4 gm. of sodium benzoate by mouth, and the output of hippuric acid for the ensuing 6 hours determined.

30 minutes the crystalline product is filtered, washed with a small amount of cold water, and dried. By using a 4.5 cm. filter paper on a 2.5 cm. filter plate, the hippuric acid can be weighed without removing it from the filter paper. Another filter paper of the same size can be used as counterweight.

To the weight of the hippuric acid, must be added the quantity remaining in solution. Approximately 0.1

gm. of hippuric acid will remain dissolved in 100 cc. of urine containing 50 gm. of ammonium sulfate. To convert the weight of hippuric acid to benzoic acid, one multiplies by 0.68. A normal adult will excrete 1.0 gm. or more of hippuric acid (equivalent to 0.68 gm. of benzoic acid) in 1 hour after receiving sodium benzoate intravenously. For convenience 1 gm. of hippuric acid can be taken as the standard for normal. This will obviate the necessity of converting the hippuric acid to benzoic acid for calculation as has been the custom in the oral test.

The intravenous modification of the hippuric acid test is not intended to replace the original oral test, but is offered as an alternate method. In the new test certain precautions must be observed. It is essential that the sodium benzoate solution be properly prepared to make it safe for intravenous use.* Furthermore the patient must be able to empty his bladder completely at the end of the test. Often it is advisable to have the patient drink a glass of water before the test to increase the volume of urine.

The accuracy of the determination of hippuric acid has been distinctly increased by adding ammonium sulfate before precipitating the acid. Weichselbaum and Probst (5) found that the solubility of hippuric acid is decreased by adding sodium chloride to the urine. Their contribution prompted the investigation of other salts, and it was found that ammonium sulfate is even better than sodium chloride.

*Ampules of sodium benzoate for the test have been prepared by Hynson, Westcott and Dunning, Baltimore, and by George A. Breon and Co., Kansas City.

SUMMARY

A technique for carrying out the intravenous modification of the hippuric acid test for liver function is described. The excretion of 1 gm. of hippuric acid in one hour after 1.77 gm. of sodium benzoate has been injected is recommended as the standard for normal.

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The Use of Pectin-Agar Mixtures in Diarrhea

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SIMPLE summer diarrhea is one of the many vexing problems which confront not only the pediatrician but the general practitioner. The literature pertinent to the subject is quite extensive yet no specific explanation or therapy is even now apparent. It is commonly stated that in infancy "hot weather, in-

fections and artificial feeding" (1) are the causative factors, but it is not the purpose of this paper to discuss etiology or to criticize methods of therapy. Certain general remarks, however, may be in order. The two most commonly employed therapeutic procedures are (1) high protein diet, or (2) starvation, with slow return to normal food intake. The use of

high protein is based on the theory that diarrhea is caused by excessive fermentation of carbohydrate with the production of lower volatile fatty acids which act as intestinal irritants. The harmful nature of such volatile fatty acids is much in doubt. Holt and McIntosh (1) say: "Restriction of the carbohydrate intake may diminish the production of these acids without curing diarrhea, and, conversely, a high carbohydrate diet does not, as a rule, produce any noticeable aggravation of the condition."

The starvation regimen, ordinarily successful, is not ideal because excessive loss of weight frequently ensues, the too prompt reintroduction of the usual formula occasionally leads to exacerbations, and the support of the mother is difficult to elicit because her whole nature demands that she feed her hungry child. It has been stated that there is an inability to digest food during diarrhea, but apparently the only evidence in support of this common belief is that food passes more rapidly through the gastro-intestinal tract. It is also of interest that this same thought was used as an argument when it was customary to starve typhoid.

Winters and Tompkins (2) in this country first suggested the use of pectin and agar in the treatment of diarrhea. Their therapy was not new, but their whole method and procedure was novel. For some years apples had been claimed valuable in treatment of diarrhea. The reasons underlying the success following their use are vague. Moro claimed the effectiveness of apples was due to tannic acid (3). Heisler would also give credit to malic acid and to the mechanical cleansing of the intestines (4), while Scheer places most emphasis on indigestible bulk (5). This latter author successfully fed "agar milk" for diarrhea (6). Malyoth (7) believes pectin and cellulose are the active agents.

Various colloidal substances (pectin, hemicellulose, agar, gums, etc.) are claimed to be effective in the treatment of diarrhea. The physical or chemical properties of such materials are used to "explain" their successful use. Principal emphasis has been placed on their ability to enmesh and cause the evacuation of bacteria (8) and toxins (9), but also their hydrophilic properties are believed to be important (10).

In examining the literature on pectin, it is interesting to note the many reasons why it is believed to be of physiologic value to the body; e.g.:

1. It is bactericidal* (13).
2. It is a source of galacturonic acid—a detoxifying mechanism (14).
3. It absorbs toxins and even poisons from the intestinal canal (9).
4. It is hydrophilic (10).
5. Its buffering action makes milk more readily digestible and should favor the growth of certain organisms (15).
6. It is soothing and healing to the inflamed and ulcerated gastro-intestinal tract (10).
7. It reduces blood coagulation time (16).
8. It helps relieve constipation (17).

Data to prove any one of these hypotheses are likewise scanty, but when all were added together it awakened our interest in the therapy of diarrhea as originally proposed by the Indianapolis investigators.

*A second publication by the Indianapolis investigators (11) attributes the sole bactericidal quality to pH rather than to any peculiar characteristic of pectin. Prickett and Miller (12) concur in this finding.

Experimental: At first we hesitated to accept the large amount of carbohydrate suggested by Winters and Tompkins. Possibly our thought in this was conditioned by the hypothesis that carbohydrate fermentation is especially culpable in diarrhea. We therefore planned to compare the effect of pectin and agar mixtures with and without added carbohydrate. Through the courtesy of the manufacturers,* we obtained a preparation similar to that employed by Winters and Tompkins, with the following composition:

<i>Preparation A</i>	
Pectin	6.3%
Agar	4.3%
Dextri-Maltose No. 1	89.4%

The other preparation employed had an identical ratio of pectin to agar, but no added Dextri-Maltose. Its composition was:

<i>Preparation B</i>	
Pectin	59.4%
Agar	40.6%

The two preparations were added to milk in quantities sufficient to supply equal amounts of pectin and agar.

All cases seen were in private practice. The majority were treated at home and hospitalization was employed only in the severe cases requiring parenteral fluids or transfusions or when the patient lived too far away. A total of 32 cases was followed on Preparation A and 16 cases on Preparation B.

Making the Formula: The preparations were made as recommended: the necessary amount of the experimental preparations (16 level tablespoonfuls of Preparation A or 2½ level tablespoonfuls of Preparation B) was placed in double boiler with a pint or 24 oz. of whole milk and cooked for 15 minutes, poured into 8 custard cups, and allowed to cool. One or more cupfuls was used at each feeding. The gel strength is greater with the smaller amount of milk, and this was used with the older children (i.e., those that had been weaned); for infants on the bottle the more dilute preparation was preferred. By enlarging the hole in the nipple the dilute formula is readily administered. For the older children, chocolate or various fruit flavors were added as desired by the mother. Because Preparation B was not particularly palatable, saccharine, gr. ½ to the pint, was ordered.

The pectin-agar and pectin-agar-Dextri-Maltose diets were started without a preliminary starvation. Water was forced, but no other food or medication was given except parenteral fluids when severe dehydration was present. No feeding by gavage was necessary. Many children requested more of the diet than was prescribed, and the mothers were instructed to supply ad libitum. Preparation A was much more popular with the children and with the mothers than Preparation B.

In prescribing each diet the mother was told that she might meet with resistance when first giving the mixture but that by adequate zeal and

*The preparations employed were supplied by Mend Johnson and Company of Evansville, Indiana. Our Preparation A is referred to by them as Laboratory Product No. 83; our Preparation B, as Laboratory Product No. 102.

urging on her part the child would probably be over the diarrhea in a day or two. The only children who initially refused the preparation were "spoiled"; the majority took it with no protest, but even with a degree of enthusiasm. The greater number of mothers in this group were well educated and only a few of the less intelligent had to be given additional moral support to continue the formula. By outlining clearly the feeding plan at the first visit one can be relieved of much annoyance in the nature of future telephone calls.

Stools were regularly forwarded from the office of the clinician (K.) to the bacteriological laboratory. For physical reasons it was not possible to obtain a

TABLE I
Classification of cases

Clinical			Bacteriological		
Diagnosis On First Examination	No. Cases		Classification	No. Cases	
	Group A	Group B		Group A	Group B
Diarrhea	18	12	<i>Escherichia</i> and others	11	8
Dysentery	14	4	<i>Salmonella</i>	4	3
			<i>Shigella</i>	4	—
			Not cultured	10	5

stool for culture from each child, but the survey accomplished gave us a fairly complete idea of the type prevalence of organisms in our community during the summer of 1938.

Results: The degree incidence of different bacterial flora in the stools is given in Table I. With the exception of the fact that no dysentery organisms were found in the stools of infants in Group B, the predominating organisms were principally of the *Escherichia* and *Salmonella* groups. Perhaps the sole value of the bacteriological studies was to show that dysentery organisms were not particularly prevalent during the study. As a fact of some interest, the clinical diagnosis on examination has been similarly recorded. As such estimates are based solely on physical findings, the figures in Table I suggest that the infants in Group A were sicker than those in Group B.

In Table II the various objective data are summarized in so far as is practical in a study of this kind. Unfortunately, and entirely by chance, the youngest infants, and those whose illness had persisted for the longest average time with the larger average number of stools were placed on Preparation A. This would confirm the similar conclusions from Table I. In spite of this the infants receiving the carbohydrate-containing preparation (A) responded better than those receiving merely the pectin-agar mixture. The only objective measure of effectiveness was the number of days after institution of therapy before normal stools appeared. Using this measure, Group B appeared slightly superior, but because diarrhea had persisted in Group A for a much longer period of time, and the infants in this group were younger, we are inclined to

discount any semblance of superiority for the B-preparation.

Three deaths were observed during this study. One child was comatose on admission to the hospital with a severe dysentery and incontinent bowels. The second child had been unsuccessfully treated for six weeks by three physicians who had finally referred the case. The diarrhea had shown great improvement just before death, which was from bronchopneumonia and inanition. The third death was due to sepsis from dermatitis gangrenosa infantum after recovery from the diarrhea.

Fever, except in the one case complicated by pyelitis, disappeared within 24 to 36 hours; dehydration, when severe, was treated with parenteral fluids, but if mild, was satisfactorily relieved by the diet alone. Excoriated buttocks healed within 36 hours in most instances. When gross blood was reported in the stools at the onset, it disappeared on the average by the 2nd day of therapy.

Several observations relative to the two preparations are pertinent:

1. In general the children took Preparation A better than B, even though saccharine was added to the latter.

2. There seemed to be less vomiting by those infants who received Preparation A, as compared with infants receiving B.

3. Mild acidosis disappeared more promptly with Preparation A than with Preparation B.

4. There was no evidence of increased fermentation (flatulence) through the use of Preparation A in spite of its high carbohydrate content.

In all cases distention disappeared on administering either of the two pectin-agar materials. As indicated in Table II, either preparation is satisfactory for the treatment of diarrhea promptly and effectively.

DISCUSSION

Normal stools are to be expected within approximately 3 days after Preparation A is incorporated in

TABLE II
Summary of cases

	Preparation A	Preparation B
Number of Cases	32	16
Av. age in months	18.7	33.3
Av. days of illness prior to treatment	6.2	1.4
Av. number of stools per day prior to treatment	9.3	6.9
Av. temperature when first seen	100.7	101.1
Av. day on which first normal stool appeared	3.2	2.4

the diet. With mild diarrhea the character of the stool will return to normal within 12 to 48 hours. This new therapy appears to be superior to other procedures because of the prompt return of the child to normal, together with the fact that there is no concomitant weight loss, and, the gradual return to full calorie intake decreases the possibility of complications.

After normal stools have returned, it is important that the transition to the regular diet be slow. When the stools appeared small, not watery, and moderately

frequent (not over 3 to 4 daily), bananas, jello, cottage cheese, or dry toast were offered at some one feeding. The following day thin soups, cereals, or skimmed milk were tried. In young infants on milk formulae the regular feedings were gradually restored via skimmed milk feedings. Children vary so much in their ability to take food that one must learn how to return a child to a full diet chiefly by experience. Naturally a return of the diarrhea calls for a prompt return to the pectin-agar diet for a day or two.

It is admittedly difficult to make a statistical comparison of diarrhea treated in different ways. Clinical impressions are sometimes more valuable in a disease of this nature than mere average figures. The senior author has had considerable experience in summer diarrhea as seen in private practice, and it is believed that this treatment offers the best approach to successful therapy. It is, of course, not a panacea for all disturbances nor is it a substitute for intelligent pediatric care, but it comes nearer to being the one satisfactory approach than any other thing yet tried.

In spite of early fears that the extra amount of carbohydrate was to be avoided, the study was concluded with the feeling that this is an added desirable feature. We adhered to the original suggestion of Winters and Tompkins and much against our early thought used whole fluid milk in all formulae. This seems to have a definite advantage. There was no evidence of inability

to use or digest the food, and in practically all the cases there was evidence of a prompt return to normal gastro-intestinal function.

Especially interesting was the rapid disappearance of toxicity. The remarkable improvement in the appearance of these children was the most outstanding feature of the study. To see a child in a moribund condition respond in 24 hours and appear almost well is a phenomenal thing even with the miracles of modern medicine. The prompt return of normal stools is most gratifying because there is not then the continual loss of body fluids through diarrhea that leads to acidosis, dehydration, and eventual complications.

CONCLUSIONS

Thirty-two cases of diarrhea seen in private practice were successfully treated with high caloric feedings consisting of whole milk, pectin, agar, and Dextri-Maltose. Comparison was made with a second group of 16 infants receiving identical formulae save for the added carbohydrate. All cases responded satisfactorily, but the addition of carbohydrate is believed to be a desirable procedure.

On the basis of past experience in the treatment of diarrhea, we believe the addition of pectin, agar, and Dextri-Maltose to a whole milk formula is a safe, effective, and satisfactory treatment.

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Perforation of a Gall Stone Into the Stomach With Resulting Pyloric Obstruction: Case Report With Gastroscopic and Surgical Findings

By

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FOREIGN bodies in the stomach are amazing for their variety. They have been discovered by clinical, roentgenological, surgical and post-mortem examinations and are usually divided into three groups: (1) swallowed objects, (2) bezoars formed within the

stomach, and (3) foreign bodies which have entered the stomach through or within the abdominal wall.

Under the last classification cases have been reported (1) of the development of a fistula between the gall bladder or a biliary duct and the stomach by the passage of a gall stone.

In this article we are reporting a case with symp-

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toms of pyloric obstruction produced by a gall stone which had passed directly from the gall bladder into the stomach.

CASE REPORT

A 62 year old married man entered the Strong Memorial Hospital on September 26, 1938. He began to have acute

crampy abdominal pains, three months previously, following the drinking of a glass of beer. Pains continued to appear intermittently from a few minutes to two hours after eating. Three weeks ago he developed flatulence and nausea. He vomited undigested food particles without blood. In the past two weeks he had vomited practically all the solid foods ingested. Medication gave no relief. His appetite fell off and he had lost 6-7 lbs.

The only past history of consequence was an attack of biliousness described as "yellow vomiting" about one year ago. In the interim he had occasional flatulence and heart burn.

The physical examination was essentially negative except for congenital clubbed feet and a large degree of brown pigment in the skin of his left leg.

Laboratory examination: Wassermann was 3+ in the cholesterol antigen, negative in the other antigens. Kahn was 3+. Stools were negative for occult blood. A gastro-intestinal roentgenographic examination on September 29, 1938, revealed on the first swallow of barium a round translucent area in the pre-pyloric region of the stomach. Peristalsis came up to this area but no waves passed by. The rugal pattern was interrupted by this defect. The



Fig. 1. Roentgenograms interpreted as benign tumor causing pyloric obstruction.



Fig. 2. Gall stone in the stomach as seen by gastroscope.

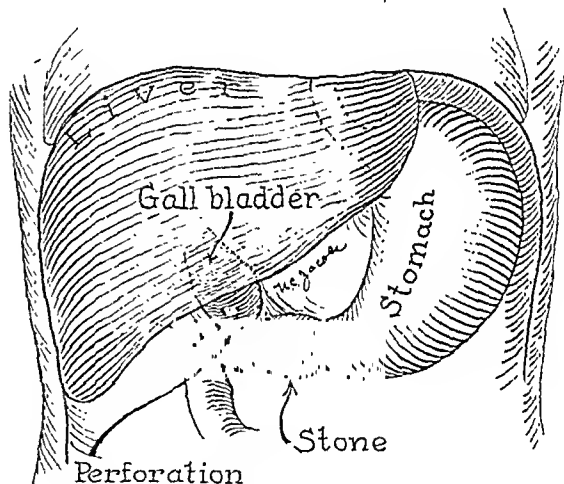


Fig. 3. Diagram shows findings present at operation.

barium then passed around this lesion, which measured about 4 cm. in diameter. The duodenal cap was not filled and the stomach was empty in four hours. The roentgenographic diagnosis was: benign type of lesion in the stomach; old duodenal ulcer (Fig. 1).

The gastro-intestinal series was repeated on October 13, 1938, with the same findings except that the observer thought that the lesion was slightly smaller in size.

Gastrosopic examination: The antral and pyloric parts of the stomach were visualized and appeared normal. A grayish-black lesion was seen in a position close to the antrum on the anterior wall near the level of the greater curvature (Fig. 2). This lesion was larger than the gastrosopic field and seemed to be free from the mucosa wherever it was visualized. The gastrosopic impression was that of a benign lesion, the exact nature of which was not known.

The patient was explored on October 14, 1938. The tumor was felt in the pyloric end of the stomach and it was at once apparent that it was a freely movable foreign body. Examination around the pyloric region revealed a gall bladder adherent on the stomach side of the pylorus (Fig. 3). The duodenum had a good deal of scar tissue

about it. A small incision was made in the stomach wall and a gall stone, about 3 cm. in diameter, was removed.

COMMENT

This is a case report of a gall stone acting as a foreign body and producing pyloric obstruction. The

gall stone had perforated from the gall bladder directly into the stomach. The perforation had become closed, allowing the gall bladder to remain adherent to the stomach wall. Apparently because of large amounts of scar tissue in the pyloric and duodenal regions, the stone was unable to pass through the pylorus. It eventually produced an intermittent pyloric obstruction.

This is probably the first report on the gastroscopic visualization of a gall stone acting as a foreign body in the stomach (2). The roentgenogram examination suggested that the lesion was located and fixed in the pyloric end of the stomach. However, the gastroscopic examination showed the body to be outside of the antrum and free from the mucosa. This apparent disagreement was probably due to the fact the gall stone was free and thus influenced by gravity and peristaltic waves. It is conceivable that food and barium with the aid of peristalsis pushed this foreign body into the pyloric end of the stomach in the attempt to pass it through the pylorus. However, in the gastroscopic position the lowest point of the stomach assumes a different level, which in some people may be at the area where this foreign body was seen with the gastro-scope.

SUMMARY

A case of gall stone acting as a foreign body in the stomach is reported. The clinical, roentgenological, gastroscopie and surgical findings are described.

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Fig. 4. Gall stone acting as foreign body. The stone was broken after its removal.

Complete Biliary Fistula of Four Years Duration With Hemorrhagic Tendency*

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WE wish to present a case of complete biliary fistula of four years duration with eventual recovery. The marked hemorrhagic tendency and prothrombin deficiency resulting from this prolonged loss of bile as well as the effects of treatment with especial reference to Vitamin K should be of interest.

M. S., a white female, age 65, was admitted to the Philadelphia General Hospital on November 9, 1938. Her complaints upon admission were (1) a draining sinus in the right upper quadrant of 4 years duration, (2) pain in the right upper quadrant, (3) stiffness of the legs of five weeks duration, and (4) purpuric spots on the extremities.

The patient was well until January, 1935, when she had an attack of right upper quadrant pain associated with jaundice, chills and constipation. She was operated upon in another hospital on February 1, 1935. A gangrenous gall bladder with bile leakage from its inferior surface

was found. The gall bladder was removed and found to contain several large stones. There was noted a large abscess on the right lobe of the liver draining from the inferior surface. The patient had a fairly smooth post-operative convalescence, except that drainage of bile through the wound continued. She was discharged on March 10, 1935.

After discharge there continued to be some jaundice and occasional chills. The patient was again hospitalized in July, 1935, with a diagnosis of biliary fistula. An X-ray following lipiodol injection was reported as showing branching shadows in the liver area interpreted as dilated hepatic ducts. At a second operation on July 24, 1935, an attempt was made to close the biliary fistula. The patient was discharged as improved on September 6, 1935. She continued to drain bile but experienced no further jaundice or chills. In November, 1937, she had rather severe bleeding from the urinary tract.

The patient was hospitalized for the third time in December, 1937, at which time there were apparently two

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Fig. 1. Lipiodol injection of biliary sinus through catheter in drainage tract.

sinus openings draining bile in the right upper quadrant. The upper sinus was injected with an opaque substance and again an X-ray showed what was believed to be dilated hepatic ducts. There was no connection apparent with the lower sinus. The patient was discharged as improved on January 22, 1938.

During the summer of 1938 she had two teeth pulled after which her gums bled for three days.

The biliary drainage from the right upper quadrant had continued from January, 1935, until her admission to the Philadelphia General Hospital November 9, 1938. Since the onset of illness the patient's weight has dropped from 186 to 126 pounds, though she states that her appetite has been good and that she has had no "indigestion" of any kind. Her stools have been clay colored since her first operation. For five weeks prior to admission, she complained of stiffness of the joints and of a dull ache in the long bones on standing. She has recently had hemorrhages from the nose and has noticed purpuric spots on the skin. Two days after admission, blood was noted in the bed pan following micturition.

On admission the principal physical findings were emaciation, loose atonic dry skin, pallor of the conjunctivae, blood pressure 84/60, a sear in the right upper quadrant in which there was a sinus draining large amounts of thin yellow-green fluid, an incisional hernia in the right upper quadrant and many purpuric spots on all extremities up to several inches in diameter. The patient's stools were clay colored.

Admission studies:

Prothrombin	— less than 1% of normal.
Prothrombin Time	— 420 seconds as compared with normal of 12.5 seconds.
Blood Phosphorous	— 4.8 mgm. per cent.
R. B. C.	— 3,000,000 per cu. mm.
Blood Platelets	— 220,000 per cu. mm.
Icterus Index	— 4.0.

The prothrombin present on this and subsequent determinations was calculated according to the method of Quick (1) and his associates. This method depends upon the clotting time of recalcified plasma to which thromboplastin has been added. The graph constructed by Quick from which prothrombin per cent may be calculated has been used, each determination being done in triplicate, using a normal control.

The administration of alfalfa extract (Vitamin K) was begun at 200 cc. per day with sodium choleate grains five,

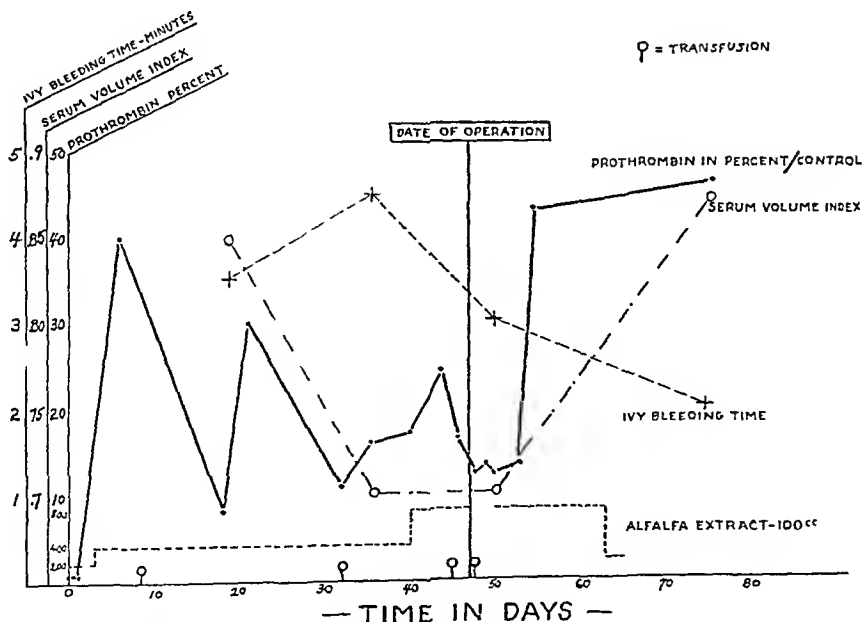


Fig. 2. Graph showing prothrombin per cent, Serum Volume Index and Ivy bleeding time.



Fig. 3. Outline of biliary tract by barium meal three months after choledochoduodenal anastomosis.

twice a day. The alfalfa extract was prepared by extraction of dried alfalfa with acetone in a Soxhlet apparatus for six to eight hours. After extraction the acetone was distilled off and the residue suspended in water. Each 200 cc. of the "Tea" represents the extraction from forty grams of dried alfalfa.

On 11-13-38 the dosage of alfalfa extract was increased to 400 cc. per day and three days later the prothrombin was 40% of control. A transfusion of 600 cc. of citrated blood was given on 11-17-38.

On 11-19-39 the patient was transferred to the Surgical Ward.

The lipiodol X-ray study on 11-21-38 was reported as showing an oval-shaped shadow approximately 1 by 4 cm. in size at the level of the 12th rib. This was interpreted as being dilated common duct. There were two or three smaller branching shadows believed to be biliary radicals or sinuses (Fig. 1).

In further studying the bleeding tendency presented by this patient it was thought that it would be of interest to observe any changes in the Ivy (2) bleeding time and in the Serum Volume Index of Boyce and McFetridge (3) and to compare these findings with the prothrombin levels. The Ivy bleeding test consists simply in observing the period of bleeding from a skin puncture while a tourniquet with a pressure of 40 mm. of mercury is in place. Any bleeding of four minutes or longer is considered a definite indication of hemorrhagic tendency.

The Serum Volume Test is a measure of clot retractility. Three cc. of blood is placed in a calibrated tube and allowed to stand at room temperature for four hours. The clot is then removed. The volume of serum remaining over one-half of the blood volume equals the index. An index

of one is normal, any reading below this being considered as progressively indicative of a tendency to hemorrhage.

The results of those comparative observations may be seen in the graph (Fig. 2).

Examination of the bile on 11-29-38 revealed: chlorides 675 mgm. per cent; cholate, 61 mgm. per cc.

On 12-12-38 the patient received a transfusion of 250 cc. of citrated blood.

On 12-20-38 the dosage of alfalfa extract was increased to 800 cc. per day with sodium cholate grains five, four times a day.

On 12-24-38 a transfusion of 200 cc. of citrated blood was given.

On 12-27-38 a choledochoduodenostomy was performed by Dr. Ferguson under local anesthesia, a number 14 catheter being placed in the original sinus tract and one Penrose drain in the operative site. The patient received a transfusion immediately after operation. She was given nothing by mouth for forty-eight hours postoperatively, fluid intake being maintained intravenously.

On 12-29-38 the patient was again started on 800 cc. of alfalfa extract daily with sodium cholate grains five, four times a day.

On the third postoperative day the dressings were soaked with bile and the catheter in the original sinus was loose. On the fifth postoperative day the light color of the drainage and some skin irritation raised the question of duodenal fistula. The patient's stools during this time remained brown, however, and by the twelfth postoperative day drainage through the wound had ceased.

The administration of alfalfa extract was stopped on 1-13-39 and the following day the patient was allowed out of bed. There had been no evidence of any hemorrhage postoperatively.

During her stay in the hospital the patient's hemoglobin had maintained a level of about 13 grams per 100 cc. The cholesterol ranged between 122 and 258, the esters usually approximating 50%. The Icterus Index ranged from four to 12.

On 1-25-39 a gastro-intestinal X-ray showed no deformity of the stomach or duodenum. On reaching the duodenum, the barium ascended rapidly into the biliary tract, outlining one large duct and two smaller ones (Fig. 3).

On 1-27-39 the patient was discharged to her family, having no abdominal or gastro-intestinal complaints, but still experiencing some difficulty in walking.

She was seen in follow-up clinic on 2-12-39. The wound was well healed and there had been no drainage. However, she still had some difficulty in walking. When seen again on 3-12-39 she was without complaint, her appetite was good and her ability to walk much improved.

On 3-29-39 Ivy bleeding time was 2½ minutes.

Prothrombin	— 58% of control
Serum Volume Index	— .8
Icterus Index	— 3
Serum Protein	— 6.5

DISCUSSION

This patient's course in the hospital presents several features of interest. She had total biliary drainage for a period of approximately four years with late but repeated bleeding manifested as urinary bleeding, bleeding from the gums, purpuric spots and joint involvement. In association with this hemorrhagic tendency our admission studies showed a very low prothrombin, less than 1 per cent, probably one of the lowest reported.

We should like to call attention to the variable effect of Vitamin K and bile salts on the blood prothrombin level in this patient. As may be seen from the graph, the determinations showed quite a marked shifting in

the prothrombin level from time to time in spite of a constantly increasing dosage of alfalfa extract and bile salts.

It may be noted that the immediate response to the administration of Vitamin K and bile salts was extremely favorable, the prothrombin rising from 1% to 40% of normal in five days. Thereafter, there was an abrupt fall never reaching the above figure until after surgical anastomosis between the duct and the duodenum. One might question the results of the test for prothrombin if the variations did not coincide very well with those noted in the Ivy bleeding time and the Serum Volume Index of Boyce and McFetridge. Certain it is that the maximum time for surgical intervention as measured by the prothrombin content of the blood came during the first week or two after the administration of Vitamin K and bile salts.

There is also shown on the graph the relationship between the Serum Volume Index and the Ivy bleeding time to the prothrombin per cent. These simple tests, the performance of which requires no elaborate equipment or special laboratory facilities, gave results rather closely paralleling the variations in prothrombin level. We believe these tests to be of value in determining the presence of a tendency to hemorrhage particularly in any circumstance where the

laboratory facilities for determination of blood prothrombin levels are not available.

This case also demonstrates the feasibility of the use of local anesthesia for major abdominal procedures in these desperately ill patients. Local infiltration with one per cent novocaine preceded by adequate pre-operative sedation proved to be perfectly satisfactory for this operation.

As may be seen from the graph, the operation was performed in the face of a low prothrombin level. This was done because we believed that the patient was losing ground in spite of constant feedings of the alfalfa extract. There was no postoperative bleeding. This may be attributed in part to the use of transfusions, though Snell, Butt and Osterberg (4) believe the effect of transfusion in raising the blood level of prothrombin is transitory. The patient received four transfusions in all, one of which was three days before operation and one immediately following it.

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Carcinoid Tumors of the Small Intestine

By

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IN 1888 Lubarsch (1) described two cases of small intestinal neoplasms situated in the submucosa. These differed from the ordinary adenocarcinomata. He studied these tumors in serial sections and found that they were connected with the crypts of Lüderkuhn. While these tumors showed lack of metastases, absence of true glandular structure and were composed of cells unlike those of normal intestinal mucosa, he still classified them as primary carcinomata of the ileum.

Ranson (2) described a similar tumor, which however extended into the mesentery and through the peritoneal coat, and was accompanied by secondary tumors in the liver, whose structure was the same as that of the primary growth. He too considered this neoplasm as belonging to the category of carcinoma. Oberndorfer (3) was the first to recognize definitely that this tumor was not a true carcinoma and called it carcinoid. He considered it to be quite harmless in character and maintained that it originated from pancreatic rests. Burkhardt (4) analyzed a group of small intestine tumors of similar type, and came to the conclusion that they were definitely derived from the intestinal epithelium and had a low degree of malignancy. Forbus (5) in an analytical review of the various theories of development, supports the endocrine theory and calls them endocrine tumors or

argentaffine tumors and maintains that they are separate and distinct from the carcinomata. In his conclusion he calls attention to the "general harmless character of the argentaffine tumors." Gaspai (6) reports a similar type of tumor but classifies it as carcinoma. Very recently Wyatt (7) again reviewed this subject, reporting three cases—two in the appendix and one in the caecum. He concludes that "this tumor is a carcinoma arising from the Kulschitzky cells of the intestinal epithelium" and "that all carcinoids are slow growing but malignant tumors." Humphreys (8) collected 152 cases of argentaffine tumor of the small intestine and found that 24.4% of them had metastasized.

Raiford (9) analyzed 29 of his own cases and found that 6 of them—over 20%—were malignant.

TABLE I

Location	Total Number	Malignant	Per Cent
Stomach	1	1	100
Small intestine	9	2	22
Appendix	17	1	5.9
Large bowel	2	2	100

In his description of the histogenesis of this neoplasm Raiford writes that "these peculiar cells were first described by Nicolas Kulschitzky (10) in 1897,

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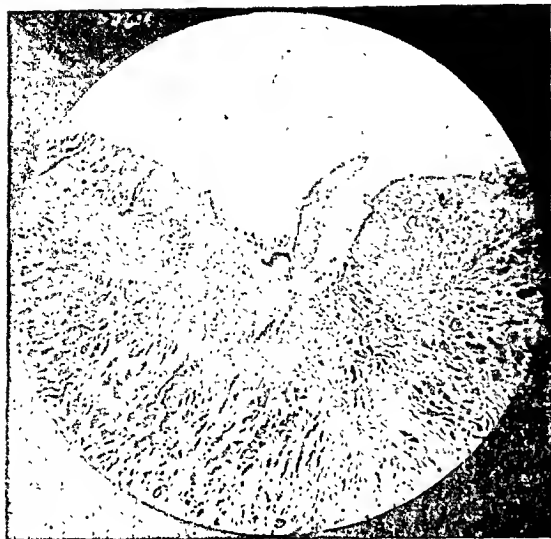


Fig. 1

as specialized epithelial cells having a characteristic structure." Schmidt restudied them in 1905 and noting their yellow color called them "gelber zellen." He concluded that they were a part of the chromaffin system and similar to the cells of the adrenal medulla. Gosset and Masson (13) found in 1914 that certain granules in the cytoplasm had the power of reducing silver compounds, having brown or black particles. In view of this affinity for silver, they called the cells "argenta-fine." By subsequent investigators they have been called "entero-chromaffine cells" (Ciaccio) (11) and "chromo-argenta-fine cells" (Cordier) (12).

The cells are found in all parts of the intestinal tract of men and many of the higher vertebrates. They differ in number with the location, being most numerous in the appendix and terminal ileum, where from five to ten may be found in each crypt. They are less common in the colon and upper small intestine and comparatively rare in the stomach and rectum. They are concentrated at the bases of the crypts, where they are pear shaped, with broad bases lying on the basement membrane and narrow bottle shaped necks leading up to the lumen of the crypt. The cytoplasm stains lighter than that of other epithelial cells, but scattered throughout are numerous acidophilic granules. The nucleus is round, uniform in size, and located near the center of the cell. It contains a finely reticulated network with numerous small chromatin particles. Stained by the silver impregnation technic of Gossett and Masson, the cytoplasmic granules appear as tiny brown or black particles.

The origin of the cells is still a moot question. Masson on the basis of their appearance in regenerating epithelium and their occasional occurrence in malignant tumors arising from the epithelial cells, attempts to explain them as differential epithelial cells of entodermal origin. Kull, studying them in the chicken embryo concluded that they were of mesenchymal origin. It seemed to Raiford that they are cells of ectodermal origin which have migrated early in life from the neural crest and become adapted to a special function in forming a part of the general

chromaffin system. In favor of this mode of origin is the striking similarity of the cells of certain tumors to the cells of the adrenal gland, not only in morphological form but also in the gross color of the tumor. The affinity for silver exhibited by tumor cells is not present in epithelial cells, but is possessed by many cells of ectodermal origin. As has already been pointed out, the appearance of rosettes in typical carcinoids links them to the neuro-blastomas.

The function of the cells is likewise unknown. Masson regards them as forming a diffuse endocrine organ and through secretion of a substance which he designates as "neurocine," exerting a regulatory influence upon the proliferation of smooth muscle fibers of the intestinal wall, especially those of the muscularis mucosa. By this he explains the smooth muscle hypertrophy coincident to the carcinoid tumors, especially those located in the appendix.

There remains the correlation of these normal argenta-fine cells with the carcinoid tumors. That these tumors arise from these cells is generally conceded. The similarity in both staining reaction and microchemical properties gives striking evidence of their relation. It is also occasionally possible to observe the growth of a tumor directly from the cells in the crypts.

Masson contends that the normal cells migrate first to nerves of the submucous plexus, where they may normally be found within the substance of the nerve. In this location, proliferation forms neuromata, and these in turn are directly responsible for subsequent tumor formation. One occasionally does find a neurogenic hypertrophy coincident with carcinoid formation and it is true there are cells in proximity to the nerves which strikingly resemble tumor cells. They are possessed however of a perineural and not an intraneural arrangement and I am not convinced that they signify more than a secondary invasion of the nerve sheath. Therefore while there is excellent reason to believe that the tumors arise from the normal argenta-fine cells, the presence of argenta-fine neuromata as intermediary stages must be questioned.

To summarize, it is ascertained beyond reasonable doubt that the carcinoid tumors arise from the cells of Kulshitzky or the chromoargenta-fine cells of Masson and that these cells are normally present in the intestinal tract of man. They are thought to be chromaffin in nature, and the tumors are consequently chromaffin tumors."

In view of the rarity of this condition and in view especially of the lack of unanimity regarding its character, it is worth while reporting these cases until sufficient data are accumulated to put this subject on a firm basis.

A. S., a woman of thirty-seven, was admitted to Beth Israel Hospital on January 28, 1938. Twelve weeks prior to this date she had begun to feel transient pains in the upper abdomen radiating to the right lower quadrant. These lasted from ten to thirty seconds, and while they were present, a mass about the size of an orange would appear to the right of the navel. Obviously a loop of bowel was contracting powerfully against an obstruction.

Occasionally the woman vomited, and as time passed the attacks of pain became more frequent. Constipation developed. Appetite disappeared, and there was a loss of 45 pounds in weight.

A diagnosis was made of intestinal obstruction, and the patient was operated on. Part of the small bowel was found then to be distended to three times the normal calibre and tracing it down obstruction was found at a place where there was a hard annular constriction. About 5 cm. distal to this point there was a small induration about 1 cm. in diameter in the wall of the small bowel. An entero-anastomosis was made, and a month later, at a second operation, the growth was resected. The pathologist reported that there were two carcinoid tumors of the jejunum, one of them causing the stenosis. There was some ulceration of the mucosa over both of them. The

patient recovered uneventfully. Fig. 1 shows the microscopic appearance of the section of the tumor.

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Editorials

SPECIAL NOTICE

THE current issue of the Journal will constitute the last number of Volume VI. The first issue of Volume VII will appear early in January and from then henceforth each volume will begin with the January issue. This will result in Volume VI being a ten issue volume. The change has been considered advisable by the Editorial Council to avoid the confusion which naturally arises when the volumes do not coincide with the calendar month. This change will make no difference to subscribers whose payments will entitle them to twelve issues.

THE LIMIT IN THE TREATMENT OF ULCER

THE last drug that any physician would ever think of using in the treatment of peptic ulcer would probably be histamine. For this reason it is interesting to find in the *Presse Médicale* for February 9, 1938, a report by Jacob and Israel to the effect that they have been getting good results in the treatment of the painful crises of ulcer by giving daily injections of 0.1 mg. of histamine. The authors started this treatment on the hunch that the good results obtained with histidine were due to the presence of histamine as a contaminant! They reported that in all the cases in which the patients were treated the pain stopped, and they concluded that this may have been due to vasodilatory effects, relaxation of smooth muscle, or to some antalgic power resident in the histamine.

We hate to suggest this because there are so many persons about with a fondness for trying new things and then writing them up enthusiastically, but really, shouldn't someone now try, at least once, to treat ulcer with a mixture of equal parts of tabasco sauce, cucumber juice, absolute alcohol and earpet taeks?

Walter C. Alvarez, Rochester, Minn.

SOME PECULIAR TRENDS IN THE INCIDENCE OF PEPTIC ULCER THROUGH THE YEARS

EVERYONE who is at all interested in the problems of peptic ulcer will want to read Alsted's little book on the changing incidence of peptic ulcer as is shown by statistics gathered through the years in the hospitals of Copenhagen. Students of the subject are well aware of the fact that years ago peptic ulcers were thought to be present almost always in the stomach and seldom in the duodenum. In Denmark, as in the United States, the ratio of duodenal to gastric ulcers has risen from about 1 to 1 to 10 or more to 1.

Doubtless much of the change of opinion which came about 1905 was due to the discovery by surgeons that duodenal ulcer was a common lesion. Actually, the pathologists did not come to realize how frequently the duodenum is scarred until Robertson and Hargis called attention to the remarkable shortening of the distance from the pylorus to the papilla of Vater which is found in every case of healed duodenal ulcer. But one can hardly ascribe all of the differences between the old and the new statistics to a defect in observation. Furthermore, although it is highly probable that much of the recent increase in the incidence of duodenal ulcer which shows up in the records of hospitals and clinics can be ascribed to the increasing frequency with which patients with indigestion are studied by roentgenologists, it is doubtful if all the increase can be explained in this way. Besides, improvements in diagnostic skill could hardly account for the marked change in the sex incidences of the two types of ulcer which has been observed in almost all countries where statistics have been gathered. Thus, during the last forty years in Denmark, the ratio of men to women with ulcer has risen from about 1 to 1 to 3 to 1.

One of the interesting points made by Alsted is that it appears that years ago ulcers were generally acute and when they healed the patient commonly remained well. Today ulcer is usually looked on as a chronic disease which will probably recur many times throughout a lifetime. One must suspect, however, that much of this difference in the aspect of the disease is artificial and due only to the change in the attitude of physicians which came with experience. Some men will remember that around 1920 many of the older gastro-enterologists and surgeons found it hard to face the fact that ulcer is a chronic disease and that the patients do not always stay well after either medical or surgical treatment. Even in the field of science, when a man hates to face a new and unwelcome fact he can often do a very thorough job of closing his eyes and mind to it.

One of the most puzzling features of Alsted's data is the decided break in the curves at a point which corresponds to the period at the end of the World War. If we could only understand what happened then to so suddenly and markedly change the incidence of hematemesis we might have a very useful therapeutic hint at our disposal.

It should alarm everyone to see how steeply the curve which represents the incidence of gastro-in-

testinal hemorrhage in men has been rising during the last few years. It is remarkable also to see how the incidence of ulcer in the case of men is rising rapidly along a straight line, while it is rising but slightly if at all in the case of women.

Walter C. Alvarez, Rochester, Minn.

NEW BOOKS ON THE EARLY DIAGNOSIS OF CANCER OF THE STOMACH

ALL gastro-enterologists will rejoice in the recent appearance of two fine books in which the authors stress the importance of studying and learning to recognize the earliest stages and appearances of cancer of the stomach. For years the textbook description of cancer of the stomach was that of the final hopeless stage with emaciation, coffee-ground vomitus, complete achlorhydria and a palpable tumor, and eventually physicians became so used to and so satisfied with this picture as to resent the writings of anyone who dared describe the picture of early cancer of the stomach as it appears in strong, healthy-looking men who complain of only a little hunger pain, or loss of appetite or strength, and who have a normal gastric acidity. When such descriptions were noticed or quoted at all, about all that was said about the writer was that he was an untrustworthy fellow who was bent on calling all sorts of lesions cancerous when they were really nothing of the sort.

Now there comes out of Germany Konjetzny's beautifully illustrated book in which the early stages of the various types of carcinoma of the stomach are described, and the work of men all over the world who have described early carcinoma of the stomach is recognized and quoted. Konjetzny writes largely from the point of view of the pathologist, and most of his illustrations show the histologic structure of gastric carcinomas of the several types. As one would expect, approximately half of the book is taken up with a discussion of conditions which are probably precancerous.

The other interesting book which is well worthy of notice here is that of René Gutmann and his associates. This book is written largely from the points of view of the clinician and the roentgenologist. Gutmann, Bertrand and Péristiany have for years been studying the early radiologic signs of cancer of the stomach, and it is a pleasure to find them admitting now that in many cases it is impossible for the roentgenologist to distinguish between a benign and a malignant ulcer. Gutmann has written a very interesting chapter on the several puzzling syndromes by which cancer of the stomach commonly announces itself. Unfortunately for our patients, those of us physicians who received our medical training thirty years ago were never told that the first sign of cancer of the stomach is often constipation, hunger pain, a little nausea, some heartburn, anemia, or loss of energy or appetite.

Submitted September 1, 1935.

Walter C. Alvarez, Rochester, Minn.

THE SIGNIFICANCE OF DUODENAL STASIS

DURING the years many articles have appeared on duodenal stasis, on the symptoms supposed to be produced by it, and on the way they can be relieved by duodenojejunostomy. Some time ago Wilkie of Scotland, was an enthusiastic advocate of this operation,

but as years passed and he saw many of his patients returning with the same old symptoms, he lost interest in the subject. Unfortunately, in most cases, the man who makes an esthustastic preliminary report about a few apparently cured patients fails to write anything later when the patients begin to come back with the same old pains and troubles.

For fifteen years the writer has hunted for a good typical case of duodenal stasis, curable by operation, but so far has not found one. Occasionally it seemed as if one had been found, but then further roentgenologic studies showed that the stasis was not repeatedly demonstrable. The writer has seen only a very few cases in which the operation was done by the home surgeon, and then the results were not encouraging. In some of these cases it became clear with the passage of time that the syndrome had really been due to a migraine in which the headache was so mild and the abdominal storm so great that it is no wonder that the correct diagnosis was missed.

In a recent paper in the April, 1939, number of "Annals of Surgery," Oppenheimer, of Beirut, reported a series of cases in which some duodenal stasis could at times be demonstrated. His studies led him to doubt the importance of pressure by the mesenteric artery on the jejunum as a cause of duodenal stasis. Neither did he find that stasis is caused commonly by adhesions, kinking, or intrinsic or extrinsic growths. Interestingly, duodenal stasis was found in students who presented none of the symptoms which are supposed to be typical of duodenal stasis, and it was not found in some cases in which the typical symptoms were complained of.

Accordingly, Oppenheimer concluded that duodenal stasis, as demonstrated roentgenographically, does not necessarily indicate anatomic obstruction, and it does not mean that the indigestion complained of is due to the peculiarity in function found.

All of this does not mean that there is no such thing as duodenal stasis with symptoms. All it suggests is that no duodenojejunostomy should be performed until repeated studies have shown that the stasis is often present and that the symptoms are not those of an atypical migraine or of a neurosis in a constitutionally inadequate person.

Walter C. Alvarez, Rochester, Minn.

THE NEW OXYGEN TREATMENT FOR MIGRAINE

IT was recently reported in the Proceedings of the Staff Meetings of The Mayo Clinic (March 15, 1939) that the administration of pure oxygen for one or two hours will, in some patients with migraine, abort the attack. The discovery was made by a layman, Mr. Charles E. Rhein, of Chicago. Further experience by Alvarez and Boothby and the reports of physicians throughout the country now leave no doubt as to the ability of this treatment to bring grateful relief to a considerable number of the sufferers with this miserable and disabling and common disease. Just how large the percentage of patients is who can be helped in this way is as yet unknown.

Curiously, cases have been found in which one headache was promptly relieved by oxygen and another, a few days later, was not. An effort must now be made to find out why some persons respond well and others do not. The impression gained is that the patients

who do not respond well are those whose migraine is atypical or complicated by other diseases such as hypertension, or by a considerable degree of psychopathy or the nervous storms of the menopause.

Experiments on animals have shown that a better oxygenation of the tissues of the brain up to a certain limit will lower the tendency to convulsive seizures, and some evidence is accumulating to show that epilepsy also can be helped by a better oxidation of the brain.

Before permitting a patient to lay out considerable money for equipment, the physician will do well first to see if he or she responds well to the inhalation of oxygen. This may be done by having the patient breathe oxygen from a small basal metabolism machine or from the anesthetist's equipment in a hospital. In the larger cities the companies that sell oxygen will often rent the necessary apparatus for a time until the patient is sure he wants to buy. If good results are secured, then the patient can buy a BLB mask (sold by the Ohio Chemical and Manufacturing Company, of Cleveland, Ohio) and can secure a tank of oxygen with a reducing valve and perhaps a flowmeter. A flow of 6 liters a minute is usually about right. The little bag on the BLB mask should about collapse with each breath. The valves on the tube between the mask and the rebreathing bag should be closed.

There need be no fear about breathing pure oxygen for a couple of hours, even two or three times a day. Especially in those bad cases in which the patient goes from one headache into another, the oxygen treatment is often better than is that with ergotamine. There

are no uncomfortable by-effects, the relief comes more quickly, and there need be no fear of injury to arteries. Interestingly, in several such bad cases, there has been a marked lessening in the severity of the attacks and in the frequency with which they recurred. This may well have been due to the fact that the patient got rest which was impossible when she was going from one horrible attack into another.

The patient should not be discouraged if the first treatment does not bring prompt and complete relief. Sometimes, at first, the brain is so irritable and tired that no treatment could put an immediate stop to the headache. Then a suppository of 3 grains (0.2 gm.) of nembatal may help greatly by quieting the vomiting center and giving the patient sleep and rest. It is useless to give drugs by mouth when nausea is present. In some bad cases intramuscular injections of gynergen will get the patient into a better condition, and then perhaps the oxygen treatment will work well. There is no known reason why the two treatments should not be used together at first. One patient who, on one day, failed to get relief from oxygen inhalation for two hours, later, when she was not so tired, obtained perfect relief in half an hour. In some of the severe cases the patient who gets relief after breathing oxygen for an hour may start to slip back after an hour or two. Then, often, another hour's treatment will put an end to the attack.

One splendid feature of the oxygen treatment is that commonly the patient comes out of the attack with a clear head and able to go right back to work.

Walter C. Alvarez, Rochester, Minn.

Book Reviews

The Wisdom of the Body. By Walter B. Cannon, New York, W. W. Norton & Company, Inc., 333 pp. Price \$3.50.

THIS is a revised edition of one of Cannon's thought producing and valuable books. One of the most remarkable things about living organisms is their ability to get back on an even keel after something rocks the boat. In this book one learns why the body is able to maintain a fairly constant supply of water, salt, sugar, proteins and fat. We learn something about the maintenance of a constant temperature and about the defenses against injurious agents. We learn something also about the ways in which the body repairs itself after illness or injury, about the value of antitoxins in disease and the ways in which the glands and the nervous system contribute to the stability of the several bodily functions.

This is a book which is of great interest not only to the professional physiologists but to the physician and even to the scientifically inclined layman. We recommend it heartily.

The Canned Food Reference Manual. New York, American Can Company, printed by The Haddon Craftsmen, Inc., 242 pp.

THIS is a splendid little book crammed with information, well written, well printed, and well illustrated. Every dietitian should have a copy on the desk. The book is full of tables giving the composition of

large numbers of canned foods, together with the content of vitamins and the more important chemical elements.

Der Magenschleim. By Arthur Mahlo, Stuttgart, Ferdinand Enke, 53 pp., 1938. Price RM 2.40.

THIS is a monograph of 53 pages on the mucus of the stomach. Much information has been gleaned from the literature, and there are brief comments on some of the author's own researches. The little monograph should be of interest to all those who have been studying the several components of gastric secretion. We have the feeling that it would have been much better if while Dr. Mahlo was at it he had gone into his subject in more detail and had presented more laboratory data. However, this booklet will be a great help to anyone trying to become oriented in this field.

Vitamin-Mineral Digest. Compiled by the Scientific Staff of the U. S. Vitamin Corporation under the guidance of Dr. Casimir Funk and Dr. Harry E. Dubin, 40 pp., 1939.

THIS booklet, published by the United States Vitamin Corporation of 250 East 43rd Street, New York, was written by Dr. Casimir Funk and Dr. Harry Dubin. Everyone knows that Dr. Funk was the man who originated the term "vitamine." In recent years the "e" has been removed so as not to confuse these

curious chemical substances with the amines. Following the question and answer style, this little book gives a great deal of information which the physician will occasionally want to have and which might take him some time to dig out of a larger volume or out of the current literature.

Physiology of the Nervous System. By J. F. Fulton. New York, Oxford University Press, 675 pp., 1938.

THIS is a splendid book and one that is much needed today. In the past, books on the nervous system have been written either from the point of view of the anatomist, or from that of the neurologist and the neurosurgeon. Now we have a book written from the point of view of a physiologist. Here Fulton brings together and summarizes an enormous amount of work which has been done during recent years on the problems of the structure and function of the nervous system. Much of this work is as yet unheard of by general practitioners and almost unknown to internists. Much of it has been done in research laboratories with apparatus borrowed from the physicist, and much of it has been done on animals in which various parts of the brain have been removed.

The part that will particularly interest the gastroenterologist will be the chapters on the autonomic division of the nervous system and on the hypothalamus with its centers for the regulation of the autonomic nervous system. It is unfortunate that during the last twenty years so much of the theorizing about the sympathetic and the parasympathetic nerves that has encumbered the literature has been done by clinicians who had only the vaguest idea of what they were talking about. One has to wonder often if they knew what the sympathetic and the parasympathetic nerves are or how they work. In most cases the writer's stock of information had apparently been that carried over from college days and from textbooks that saw the light some thirty years ago.

Of late the conception of autonomic action has been greatly changed by the discovery that out of the ends of these nerves come chemical substances which profoundly affect not only smooth muscle and other tissues but also the consciousness of the individual. Much information is being gathered also on the important subject of the relation of the autonomic nervous system to the transmission of pain, and especially of the type of pain that brings much worry to the internist.

Any clinician who will read Fulton's Chapter 13 on the hypothalamus must, we believe, be greatly impressed with the probability that some of the curious distresses which so alarm nervous and psychopathic persons are the result of disturbances in the functions of the hypothalamus. This is the place in which highly organized vegetative functions are integrated. By stimulating this region one can produce marked sweating, vasoconstriction, or changes in blood pressure throughout the body. By injury to this region, one can produce changes in body temperature, changes in the level of blood sugar, changes in blood pressure, in water balance, in the metabolism of carbohydrates and fats, and in sexual development. It is a remarkable fact shown particularly by Bard that when cerebral control is removed from this hypothalamic region, the animals will exhibit outbursts of fear or rage during which the pupils dilate, the hair stands on end, the

heart rate increases, blood pressure rises and salivation occurs. Obviously some sort of a storm takes place in the autonomic nervous system. Some experimenters have shown that these animals develop also extrasystoles and other disturbances of cardiac function.

It is interesting also that barbituric acid and anesthetics greatly affect these nuclei. The gastroenterologist must be greatly interested in this region because stimulation of these centers will markedly affect the motor and secretory functions of the stomach and intestine. It is known also that injury in this region will give rise to ulceration of the stomach and duodenum.

Already it is possible to recognize five distinct syndromes arising in the hypothalamus, four due to destruction of areas and one due to periodic irritation of the centers. These syndromes are (1) hyperthermia, (2) diabetes insipidus and emaciation, (3) the adiposogenital syndrome, (4) hypersomnia with disturbed thermal regulation and (5) autonomic epilepsy. Today it is known that diabetes insipidus is produced by a certain lesion of the anterior nuclei of the hypothalamus. Similarly, the work of Philip Smith and others has shown that one type of the adiposogenital syndrome is produced by disease in the middle group of hypothalamic nuclei. As one would expect then, patients with this type of trouble can not be much helped by the injection of pituitary substance.

The clinician must be greatly interested in this region also because it has so much to do with disturbances of sleep and with the reaction of the patient to barbiturates. As one might expect, it is this part of the brain which is particularly involved in many cases of encephalitis. There is some center in this region of the hypothalamus which suppresses cortical activity and gives rise to epileptoid spells.

The State of California, a Medico-Geographical Account. By J. Praslow. Translated from the German by Frederick Cordes. John J. Newbegin, San Francisco, 86 pp., 1939.

THIS is an interesting little book. It is naturally of particular interest to Californians, but any physician who is interested in history and exploration will find it good reading. Five years ago Dr. Cordes happened to note in a catalogue of rare books a title which interested him. He sent for the little volume and soon was busy translating it into English and learning all he could about the author, who practiced medicine in San Francisco from 1849 to 1856. After a trip back to Germany he went to Culiacan on the west coast of Mexico and practiced there until his death.

The book gives much interesting information about the appearance of California in the early days, about the Indians and the miners, and about the bad health conditions due to poor food and water. When Dr. Praslow arrived in San Francisco he found some fifteen or twenty physicians already there. There were no pharmacies at first, and every doctor had to dispense.

Praslow was much interested in the ever-present problem of scurvy. Ships coming around the Horn were generally full of it, and on landing, the patients were given large amounts of meat, many vegetables, dried fruits, and solutions of vinegar. Tartaric, citric,

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sulphuric and muriatic acids were given, also scurvy grass. The best remedy proved to be potatoes, scraped and eaten raw or applied as poultices over the swellings and ulcers. Brewer's yeast was also used.

In San Francisco there were severe epidemics of dysentery and diarrhea and at times probably cholera. Miners who went up through the swampy central valleys suffered severely with malaria. Typhoid fever was also a problem. Great numbers of Chinese were brought in from the Orient, carrying their diseases with them. Their prostitutes brought a particularly virulent type of syphilis and gonorrhea.

It is interesting to note that the Indians of the Sacramento Valley were much troubled with malaria. One wonders if they had it before the whites came.

According to Praslow, cretinism was rather common among the Indians and native-born Spaniards, especially in the neighborhood of Cape Mendocino. Interestingly, this region is still an endemic focus of thyroid disease.

Tuberculose de Tube Digestif. By André Cade, Paul Santy and Jean Heitz, Paris, G. Doin & Cie., 411 pp., 1937. Price 80 Fr.

This is an excellent monograph on

tuberculosis of the digestive tract, well written and well illustrated. There is a large bibliography. It is probable that some of the lesions described under tuberculosis of the terminal ileum fall in the group of troubles now known as terminal ileitis. This book is well worthy of a place in the library of the gastroenterologist.

Abstracts

FRIEDMAN, M. H. F.

Gastric Secretion in Birds. J. Cell. and Comp. Physiol., 13:219-234, April, 1939.

In pigeons and chickens under Nembutal anesthesia gastric secretion is intermittent, not spontaneous or continuous. In both the pigeon and the chicken the secretion of acid and of pepsin is under the control of the parasympathetic nervous system. In birds, histamine stimulates chiefly the secretion of acid, the gastric juice being extremely poor in pepsin. The concentration of pepsin is higher in the gastric juice of the chicken than in that of the pigeon. The rate of gastric secretion is dependent on the volume of body fluids in the circulation. Repeated injections of large doses of histamine cause hemorrhagic lesions of the proventriculus in the form of multiple erosions.

W. C. Alvarez, Rochester, Minn.

WEINSTEIN, LOUIS AND BOGIN, MAXWELL.

The Effect of Banana Feeding on the Intestinal Flora and on Constipation in Children and Adults. Rev. Gastroent., 6(1):12-21, 1939.

Studies were made on persons having predominating *E. coli* but no *L. acidophilus* in the feces and whose constipation did not respond to ordinary therapeutic measures. Diet was unchanged except for the addition of 3-4 ripe bananas a day. *L. acidophilus* appeared after the first week. By the end of the second week it constituted 90-95 per cent of the flora in some cases. After the sixth week it had disappeared in all but one person. Constipation was completely relieved in 1-2 weeks.—G. H. C. (courtesy of Biological Abstracts).

SNYDER, C. D., JOHNSON, R. E. AND PEEK, C. Mcl.

The Minute-Volume Uptake and Output of Substances Perfused Through Liver Surviving in an Oncometer. Am. J. Physiol., 124(3):704-716, 1938.

Analyses of the inflow and outflow to a liver preparation surviving in an oncometer have been made for K,



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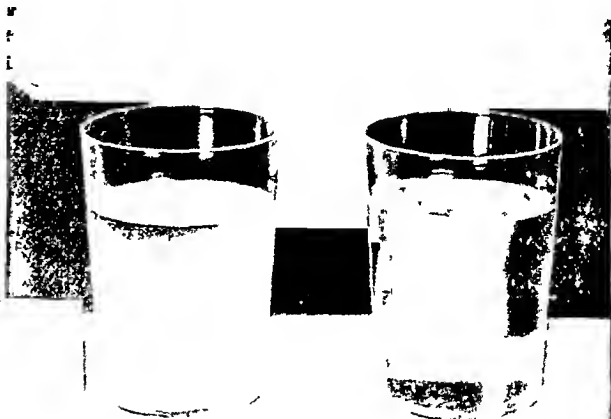


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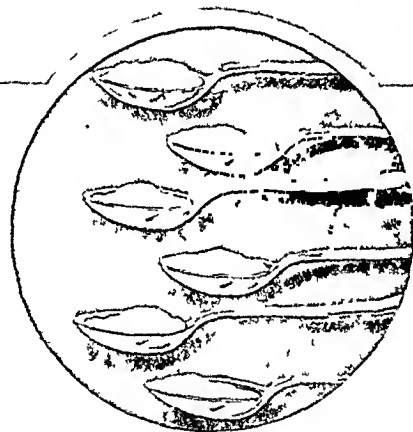
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sugar and, in a few experiments, also for chloride. The samples analyzed were collected from the hepatic outflow at frequent, successive and short-lasting intervals of time while the organ was responding to injections of acetyl-B-methylcholine chloride or adrenalin chloride into its inflow cannula. When the changes in volume of the organ as well as changes in rate of outflow and inflow are taken into the calculations, then the amounts of uptake and output of substances contained in the perfusate may be quite different from those indicated by concentrations alone at the sites of inflow and outflow. The differences in

content per unit of time under certain conditions may be all out of proportion to the differences in content per unit of volume, and the values for the former may change greatly while those for the latter change not at all and vice versa. The method obviates resort of the procedure employed in chronic cases, namely, the taking of sections out of the organ under investigation. The method further makes possible the exptl. differentiation between the vascular and glandular effects of various agents upon the liver. The experiments here reported demonstrate this differentiating capacity of the method, especially when

autonomametic agents are injected into the portal vein of the liver. The method promises further to be useful both in the study of the role played by an organ in producing transient alterations in the composition of the general circulation (minute-volume output here is of the greatest importance); and in the study of the role played by the varying contents of the general circulation, or of affluent nutritive fluids, upon the organ itself in both its vascular and glandular responses.—Author (courtesy of Biological Abstracts).

WINDLE, W. F. AND BISHOP, C. L.

Prenatal Intestinal Movements in Anoxemia. Proc. Soc. Exp. Biol. and Med., 40(1):2-4, 1939.

Gastro-intestinal movements were observed in fetuses delivered by experimental Caesarian section without anesthesia and with placental circulation intact in cats previously de-aerated. Propagation peristalsis occurred when the umbilical vein blood was less than half saturated with oxygen. Marked anoxia led to rhythmic segmentation. Profound asphyxia resulted in pendulous writhing of intestinal loops with loss of tonus.—Authors (courtesy of Biological Abstracts).

BURNSTEIN, C. L.

Effect of Some Short-Acting Barbituric Acid Derivatives on Intestinal Activity in Vivo. Proc. Soc. Exp. Biol. and Med., 40(1): 122-124, 1939.

The action on intestinal activity of some of the barbituric acid derivatives most commonly employed for intravenous anesthesia (evipal, pentothal, nembutal, amytal and sodium thioethamyl) was studied in dogs with Thirty-Vella fistulas of the jejunum. After a transitory immediate effect (5 to 15 minutes) characterized by depression of rhythmic intestinal contractions and tonus there followed a more prolonged period (10 minutes to 2 hours) in which the intestinal contractions and tonus were increased markedly above normal.—C. L. B. (courtesy of Biological Abstracts).

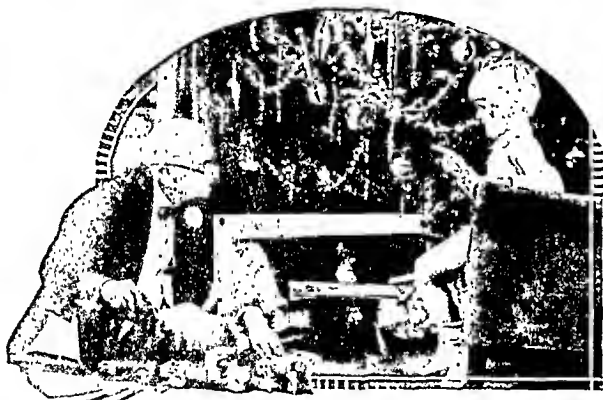
GORHAM, FRANK W. AND IVY, ANDREW CONWAY.

General Function of the Gall Bladder from the Evolutionary Standpoint. Field Mus. Nat. Hist. Publ. 417, Zool. Ser., 22(3):159-213, 1 fig., 1938.

A survey of the invertebrates for the occurrence of the gall bladder is presented. The gall bladder is a primitive organ peculiar to the Chordata. It serves the purpose of storing bile for digestion and the regulation of pressure in the biliary passages. It is uniformly present in amphibians

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and reptiles, in the monotremes and marsupials. It has been lost to some extent in those mammals which eat continuously or manifest continuous digestion, as in the herbivora, and is retained in those which tend to eat intermittently and possess a liver which forms small quantities of bile. Those mammalian spp. most closely related to the primitive stem retain the gall bladder; other orders vary. Some spp. such as the guinea pig, rabbit and cow possess a gall bladder, which does not concentrate well and hence stores very little of the total output of bile. In these spp. the gall

bladder can serve only as a pressure regulating mechanism. It appears that a sphincter of Oddi (sphincter choledochus) must have appeared in the evolutionary process concomitantly with a gall bladder since a sphincter is requisite for gall bladder filling and at the same time necessitates a pressure regulating device. Animals without a gall bladder possess no sphincter to prevent intestinal contents from regurgitation into the bile duct. Extensive tables and bibliography are appended.—K. K. J. (courtesy of Biological Abstracts).

GULZOW, M. UND AFENDULIS, TH. C.
Über die Stauungsgastritis. Tierexperimentelle Untersuchungen. Zeitschr. Ges. Exp. Med., 104(4): 465-488, 15 fig., 1938.

Acute congestion by ligation of the portal vein immediately above its junction with the pancreaticoduodenal vein, caused death of the experimental animals 2-5 hours after the operation (hemorrhage, edema, extreme distension of the gastric blood vessels). Chronic congestion was produced in 12 dogs after previous application of a gastric fistula by gradual narrowing of the lumen of the portal vein; the second part of the operation was carried out after 3 weeks in order to eliminate at this time the formation of a possible collateral circulation. The acidity of the gastric content showed a decrease, accompanied by a decrease in secretion and time of emptying, which was followed by an increase after 1-2 weeks. The gastroscopic picture, showed first venous congestion, followed by an erosive-hemorrhagic fibrinous hypertrophic gastritis. Ulcers did not develop regularly. Increase in histamin content of the portal and peripheral veins could be demonstrated by typical drop in the cat's blood pressure; the histamin formation was due to anoxemia, disturbed intestinal function, insufficient detoxifying ability of the damaged liver. Assumedly, histamin and related substances were of importance for the etiology of the gastritis which was of hematogenic toxic origin.—M. S. (courtesy of Biological Abstracts).

BING, J. AND BROAGER, B.

Investigations of the Effects of Nicotinic Acid on Two Patients with Idiopathic Steatorrhea (Sprue). Acta Med. Scand., 97 (5/6):561-577, 3 figs., 1938.

The amount and water content of the faeces were altered, but with no increased absorption of dry substance, lipid, nitrogen, Ca or ascorbic acid. On suspending treatment the diarrhea returned. None of the many other sprue symptoms was so distinctly modified as the diarrhea.—M. G. C. I.—(courtesy of Biological Abstracts).

IRWIN, MARGARET HOUSE, WEBER, JANET, STEENBOCK, H. AND GODFREY, T. M.

The Influence of Hydrogenation and Oxidation of Fats Upon the Rate of Absorption. Am. J. Physiol., 124(3):800-803, 1938.

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● It was early recognized that vitamin A deprivation in animals resulted in cessation of growth or—if long continued—in the appearance of a characteristic eye condition known as xerophthalmia (1). These two pathologic effects were both utilized in the first methods proposed for quantitative estimation of this essential food factor.

The earliest techniques for determination of vitamin A were similar in that they all first provided for depletion of the body stores of vitamin A of the rat by restriction of the animals to basal rations free from or quite deficient in the vitamin. In the "rat growth" method, the vitamin A activity of the material under assay was estimated by feeding graded dosages to animals depleted of the vitamin (as gauged by cessation of growth) and recording the ensuing growth response (2). In the "curative technique," the incidence of xerophthalmia served as the criterion of vitamin A depletion (3), and vitamin A activity was estimated by determining the dosage of the test material necessary to establish cure of xerophthalmia.

Techniques were also gradually developed which in some instances embodied features of both the growth and curative methods. Still another technique based on the continuous appearance of cornified epithelial cells in vaginal smears—a further characteristic of vitamin A deficiency in female rats—was evolved (4). Further research showed that colorimetric and spectrographic methods may be adapted to the estimation of vitamin A activities of specific materials (5).

Of all methods for estimation of vitamin A in foods, the rat growth technique appears to be favored today (6). Gradual improvements and refinements—as well as recognition of the existence of provitamins A—have led to development of the growth method now included in the U. S. Pharmacopeia XI. This method requires that young rats weighing 10 to 50 grams (at an age not exceeding 28 days when placed on a vitamin A deficient ration) shall manifest symptoms characteristic of vitamin A deficiency within a period of 25 to 45 days. Rats properly depleted of vitamin A reserve are assembled in negative control groups receiving no supplement, reference groups receiving graded doses of the standard reference material, and assay groups receiving graded doses of the assay material. During the ensuing period of not less than 28 days, the test animals are fed daily doses of the proper supplement. The body weights of the animals are recorded at frequent intervals during and at the end of the assay period. From the average gains in body weight of rats in the assay and reference groups, dosages of assay and reference materials, and the vitamin A activity of the standard of reference, the vitamin A activity of the assay material is calculated.

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- (1) 1913 J Biol Chem 16 473 and 255
- (2) 1918 J Biol Chem 66 1
- (3) 1931 J Dairy Sci 14 779
- (4) 1927 J Biol Chem 73 153
- (5) 1938 J Am Med Assoc 111 725

- (6) 1936 The Pharmacopeia of the United States, Eleventh Decennial Revision page 478
- (7) 1929 Ind Eng Chem 21 347
- 1936 J Am Diet Assoc 12 231
- 1936 Mass Agr Expt Sta Bull No 338
- 1938 Nutrition Abstracts and Reviews 8 281

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melting points exceeded body temperature the rate of absorption was progressively reduced. Hydrogenated cottonseed oil oxidized by aeration but of practically constant melting point was absorbed at a decreasing rate with increasing peroxide number.—H. S. (courtesy of Biological Abstracts).

BAGGENSTOSS, ARCHIE H.

Major Duodenal Papilla: Variations of Pathologic Interest and Lesions of the Mucosa. Arch. Path., 26(4):853-868, 3 figs., 1938.

An investigation at the Mayo Clinic of 100 major duodenal papillae of man disclosed the following findings

of pathologic interest—a junction of bile duct and pancreatic duct occurred in 33 of 55 specimens examined and in only 6 of these specimens was the ampulla 5 mm. or more in length; marked narrowing of the bile and pancreatic ducts occurred as they pierced the duodenal wall; polyps of the papilla were found in 4 of the 100 specimens. Lesions of the major duodenal papilla which have been observed in routine postmortem examinations at the clinic, up to October 1, 1936, include two cases of ulceration, 2 cases of edema, 25 cases of polyp and 28 cases of carcinoma (0.21 per cent). In 15 cases of carcinoma of the major papilla, there was no evi-

dence of metastasis. 3 cases of carcinoma of the minor papilla were also observed.—A. H. B. (courtesy of Biological Abstracts).

CAMERON, G. R. AND DE SARUM, G. S. W.

The Effect of Liver Damage on the Action of Some Barbiturates. J. Path. and Bact., 48(1):49-54, 1939.

Rats with acute liver damage are more susceptible than normal animals to the quickly acting barbiturates, pentobarbital Na and evipan Na. This effect quickly passes off when liver regeneration sets in. With progressive, liver damage, as in the pre-cirrhotic stage of CCl₄ cirrhosis, the action of pentobarbital Na is greatly enhanced long before serious structural damage has appeared in the liver. It is suggested that impairment in detoxifying function precedes the development of cirrhosis.—Authors (courtesy of Biological Abstracts).

GOODPASTURE, W. CARTER, VERNEULEN, DONOVAN, PAUL B. AND DRAGSTEDT, LESTER R.

The Bromsulphalein Liver Function Test as a Method of Assay of Lipoeaic. Am. J. Physiol., 124(3):642-646, 1938.

Impaired liver function as evidenced by abnormal retention of bromsulphalein has been found in the large majority of insulin-treated depancreatized dogs that develop fatty infiltration in the liver. The disturbance in liver function was found to be roughly proportionate to the amount of fatty infiltration and was promptly corrected by lipoeaic administration. Accordingly, the bromsulphalein test was suggested as an additional criterion of lipoeaic deficiency in depancreatized dogs and possibly also in diabetes mellitus.—Authors (courtesy of Biological Abstracts).

BELL, E. T.

A Clinical and Pathological Study of Subacute and Chronic Glomerulonephritis, Including Lipoid Nephrosis. Am. P. Path., XIV, 6, p. 691, Nov., 1938.

This report represents a study of 181 cases of subacute and chronic glomerulonephritis which have been classified in accordance with certain clinical and pathological features into the following groups:

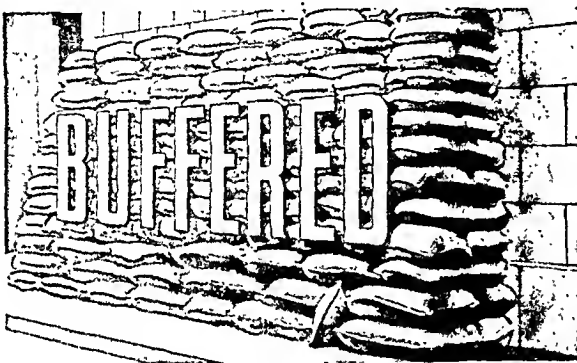
I. Subacute glomerulonephritis.

II. Chronic glomerulonephritis in which death was due to an intercurrent disease.

III. Advanced chronic glomerulonephritis of azotemic type.

A. With history of acute glomerulonephritis.

B. No history of acute nephritis,



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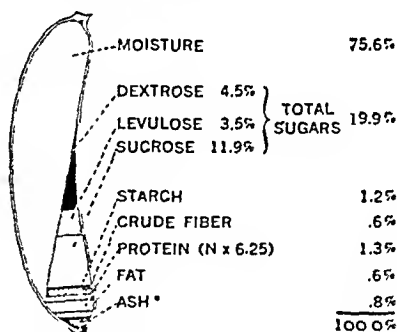
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Vitamin content
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Convalescent Diets

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the kidneys weighing 250 gm. or more.

C. No history of acute nephritis, the kidneys weighing less than 250 gms.

IV. Chronic glomerulonephritis of the hydropic type.

A. With glomerular structure of chronic proliferative glomerulonephritis.

B. With a glomerular structure largely membranous but partly of proliferative type.

C. With a normal glomerular structure or a strictly membranous glomerulitis.

Subacute glomerulonephritis. This group blends from the acute into the chronic type. Cases terminating in uremia after a few months are called subacute. The kidneys are normal in size or enlarged. There is severe uniform obstruction of all the glomeruli, but there are no hyaline glomeruli. There is moderate uniform atrophy of the tubules; there is very little atrophy in the acute type. In the chronic type there are patches of extremely atrophic tubules associated with hyaline glomeruli.

The blood pressure is usually high. Retinal edema and hemorrhages are frequent. Abundant albumin and

casts are found in the urine, but hematuria is infrequent. Edema is usually marked and the plasma proteins low. Death was due to uremia in all of the author's cases.

The pathogenesis of the glomerular lesion in chronic glomerulonephritis may be traced much as follows. The normal glomerular lobule is composed of capillaries with a distinct basement membrane in both inner and outer walls. In acute glomerulitis there is an increase of endothelial cells and the central basement membranes of the capillaries are split into numerous irregular fragments—intracapillary fibres. In severe glomerulitis the capillaries are completely obstructed but in less severe lesions from which the chronic forms probably develop, the capillaries are not closed completely. As the inflammation subsides the blood forces the intracapillary fibres to the center of the lobule where they become fused to form a central hyaline mass. If the capillaries are completely closed during the acute attack the glomerulus becomes hyaline. The chief difference between the early and mild lesion and the advanced azotemic type is the difference in the number of hyalinized glomeruli. The advance from the early to the late stage of chronic glomerulonephritis is probably due to repeated acute attacks which obstruct more and more of the glomerular circulation.

The total course of the disease in advanced glomerulonephritis of the azotemic type varied in the author's series between 18 months and 26 years; the average being 10 years. The acute attack is usually followed by a latent period when the patient considers himself well. The acute attack may have been severe, or so mild as to have been overlooked. There may be repeated acute exacerbations during which all symptoms become more intense. The blood pressure is usually somewhat elevated, 150 mm. hg., to become higher toward the end of the disease. In a few cases going on to death no elevation of blood pressure has been noted; and in others very high pressures, 275 mm. hg. have been recorded. The average weight of the heart was 456 gm. It varied from 200 to 700 gms. The hypertrophy was of the left ventricle. The renal function remained fairly stationary, 25 to 50 mg. per cent blood urea nitrogen—until the terminal stages when it failed rapidly. When the urea nitrogen reached a level of 100 mg. per cent the patient lived usually but a few weeks. The phenolsulphonephthalein test ran parallel with the urea nitrogen. Hypochromic anemia was usually present as was also retinal exudates and hemorrhages. Edema varied

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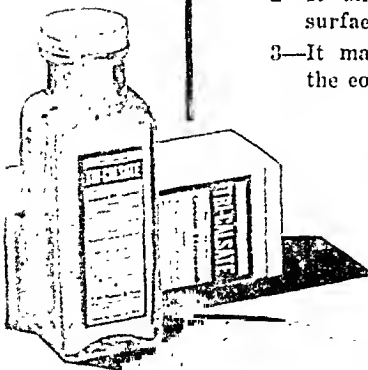
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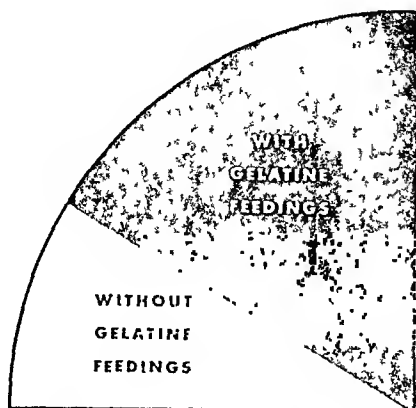


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'Proceedings of the Society for Experimental Biology and Medicine', 40 157, 1939.

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greatly in different cases, often present in the acute beginning to disappear later, but sometimes only present at the end. It depends probably more on the level of the plasma proteins than other factors. There was no apparent relation between edema and the size of the kidney in this group. There was also no definite relation between the size of the kidney and other clinical features, as the heart size and the blood pressure. As a rule a continued edema usually accompanied a large kidney.

The variations in the size of the kidneys in the terminal stages of chronic glomerulonephritis were re-

lated to the structural changes that had taken place.

In acute glomerulitis the capillaries show lesions ranging from no obstruction at all to complete obliteration. When the glomeruli have suffered no or little narrowing, glomerular filtration continues and the tubules are unaffected, but when the capillaries are closed the glomerulus becomes hyaline and the tubules disappear entirely or become epithelial cords. The degree of kidney atrophy corresponds to the degree of the glomerular involvement. When many glomeruli are partially damaged and the corresponding tubules are only

partially affected renal insufficiency may result without the kidney having undergone any contraction.

The most common form of chronic glomerulonephritis is the small contracted kidney of usually less than 200 gm. weight. The cortex is thin and the majority of the glomeruli are hyaline and their tubules have almost disappeared. Eighty to 90 per cent of the visible glomeruli are hyaline and many have probably been absorbed by phagocytes. A terminal acute glomerulonephritis is at times found superimposed on a chronic form, as these glomeruli then show fresh epithelial crescents and other acute changes. When arteriosclerosis is associated with the chronic lesion a very high blood pressure has previously existed. In the group of chronic glomerulonephritis in which the kidney is of normal or even of greater than normal weight, the number of hyaline glomeruli present is less than one-half of the total number seen, and may be as few as 10 or 20 per cent. The most frequent nephron in these large kidneys is a damaged glomerulus with moderate atrophy of its tubule. The renal cortex then is not much shrunken. Arteriosclerosis may likewise be associated at times with this form of nephritis. As damaged glomeruli and tubules have a reduced functional capacity uremia may develop, as it does in the sub-acute type, before a large number of glomeruli have become hyaline. It is probable that repeated infections are responsible for the progressive failure of renal function in chronic nephritis.

In chronic glomerulonephritis of the hydropic type edema was a prominent feature throughout the greater course of the disease. Both edema and albuminuria increased, however, at times in the form of acute exacerbations. The author describes three subgroups of this form of nephritis, all lipid nephrosis in a clinical sense, but differentiated one from the other by histological differences in the structure of the glomeruli. The first subgroup histologically was a chronic proliferative glomerulonephritis in which death occurred from edema early in the disease. The kidneys were large, yellowish tinged on section and smooth surfaced. All glomeruli were enlarged and uniformly involved. The lobules showed central masses of hyaline formed by thickening and fusion of the centrally placed capillary basement membranes. There was no diffuse thickening of the capillary basement membranes of the glomeruli, which characterizes most cases of lipid nephrosis. Thus chronic proliferative glomerulonephritis may reproduce the clinical syndrome called "lipid nephrosis."

The second subgroup presented the clinical picture of lipid nephrosis,



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but added to it was some hypertension, some azotemia and one patient died of uremia. The histological glomerular picture was partly of the membranous and partly of the proliferative type. They were mainly large with many permeable capillaries; there were only a few hyaline glomeruli present. The membranous type predominated over the proliferative type.

In the third subgroup with the clinical diagnosis of lipid nephrosis the glomeruli showed no evidence of proliferative glomerulitis. In 6 of the cases there was no visible change in the glomeruli whatsoever, although

there was a little elevation of blood pressure, but not progressive, and a little decrease in renal function. Those cases with elevation of blood pressure usually showed thickened basement membranes in the glomeruli. Aside from this there was no difference clinically in the cases without any change in the basement membranes from those with patchy thickening or with marked thickening. The plasma proteins were markedly reduced; and cardiac failure played no role in the edema formation. Four deaths occurred from uremia and 17 out of 25 from infectious processes. In a tabulation of

53 cases from the literature 42 died from peritonitis. Exacerbations and remissions occurred during the course of the disease. The former often followed an upper respiratory infection. Histologically there is no primary tubular atrophy. Atrophy of the tubules occurs only when the capillaries of their associated glomeruli are obstructed. Lipoid nephrosis, therefore, is not a primary tubular disease. In young children in which the capillary basement membranes show little or no structural changes it must be believed that they have nevertheless suffered damage because all gradations of membrane changes are found as the patients become older. The thickening of the membranes in some way appear to be related to age. The convoluted tubules often contain droplets of lipid, but they never show primary degeneration or necrosis. Atrophy of the tubules in lipid nephrosis, as in the other forms, follows closure of the glomerular capillaries. It is due to primary glomerular disease and not to primary tubular degeneration as Th. Fahr maintained. Uremia may develop in the case in which there is partial closure of the capillaries causing a diffuse tubular atrophy of moderate degree, as well as in the case with shrunken kidneys from hyalinization and absorption of many glomeruli.

In conclusion the author discusses the historic development of the subject of nephritis, laying special stress upon the theories of Volhard and Fahr. However, he maintains with complete logic that the various forms of glomerulonephritis, among which lipid nephrosis is included, depend upon the extent and character of their glomerular lesions. If the initial acute attack is severe and causes widespread capillary obstruction, renal insufficiency soon develops. If death occurs in a few months from uremia it is called acute; if in 4 months to a year it is called subacute. When the initial glomerular injury is less severe so that the majority of the capillaries remain permeable a chronic nephritis develops. Complete anatomic recovery may occur after mild acute injury. The initial glomerular lesion consists of an increase of endothelial cells and splitting and fragmentation of the central capillary basement membranes in the interior of the lobules. If the capillaries become completely occluded the glomerulus becomes hyaline; if partially occluded a peripheral circulation develops in the lobule and the hyaline fibers, derivatives from the central membranes, become fused into a hyaline mass at the center of the lobule. Azotemic glomer-

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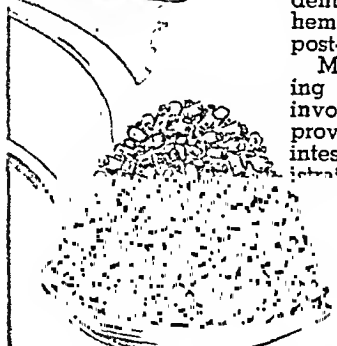
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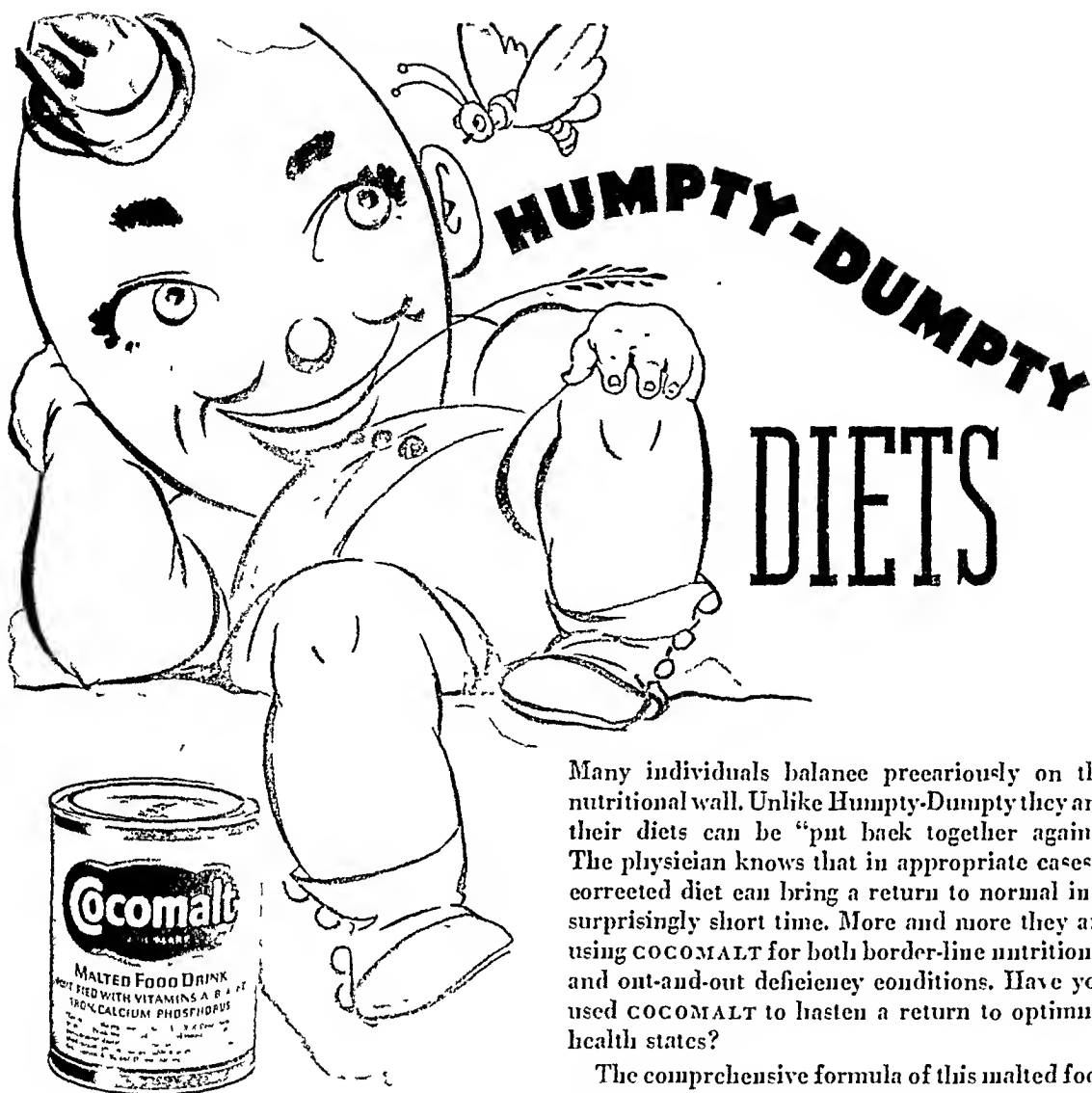
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ulonephritis is characterized by widespread obstruction of the glomerular capillaries. In hydropic glomerulonephritis the capillary walls are injured but the lumens remain open. This lesion is characteristic of membranous glomerulitis. The hydropic form rarely occurs in proliferative glomerulitis. It is not known whether the same etiologic factors produce the two forms or not; it is known only that proliferative glomerulitis blocks the capillaries whereas the membranous type permits an escape of the plasma proteins. This permeability of the capillaries causes edema, the out-

standing feature of the disease. Hypertension does not develop until the thickened membranes have produced a definite narrowing of the capillary lumens. In brief, therefore, azotemic nephritis is due to capillary obstruction and hydropic nephritis results from increased permeability of the capillaries to proteins. Azotemia develops regularly in proliferative glomerulitis but infrequently in the hydropic form. Hydropic glomerulonephritis is usually due to membranous glomerulitis, but occasionally is seen with the proliferative form.

N. W. Jones, Portland, Oregon.

BOLDYREFF, W. N.

The Pavlov Gastric Pouch. Some Historical Data. From the Pavlov Physiological Institute of the Battle Creek Sanitarium, Battle Creek, Michigan.

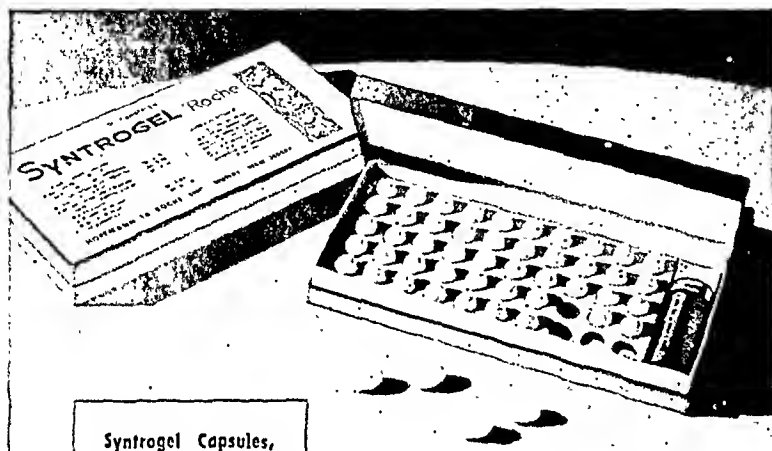
This article is prompted by the recent publication of Jemerin and Hollander (1) who properly pointed out that in some cases Pavlov pouches, as made, are really Heidenhain pouches in that they have little or no vagal nerve supply. This is due to the way in which the various branches of the vagus nerves spread over the external surface of the stomach. Jemerin and Hollander's work is important because it emphasizes the necessity of preserving an adequate nerve supply to the isolated bit of stomach if it is to be looked on as a Pavlov pouch.

I thought it might be of interest to record here some of the early historical facts about these pouches which I happen to know because I spent a number of years in Pavlov's Institute during the time in which he was so interested in the physiology of gastric secretion.

The real pioneer in the recognition and utilization of a new method for the study of gastric physiology was Beaumont (3). The gastric fistula method used by him was employed in dogs by Bassoff (Moscow, 1840) (4) and Blondlot (Paris, 1842) (5). Thiry in 1864 isolated a loop of intestine for study. This appears to have been the first effort to isolate a portion of an organ and leave it in situ for study. Klemensiewicz (6) in 1875 prepared a pouch of the pyloric portion of the stomach. This work was followed in 1878 by the production of an isolated pouch of the fundic portion of the stomach by R. Heidenhain (2). His operation is simple and easily performed. Pavlov (7), recognizing disadvantages due to the absence of a vagal innervation to the Heidenhain pouch, in 1894 introduced, with the help of P. P. Higin (8) or Khigine, his well-known method for making a pouch with most of the vagal nerve supply intact (7). In 1905 Cade and Latarjet (9) studied gastric secretion secured from a pouch accidentally made in a man.

Many persons who attempted to make Pavlov pouches failed, and some doubtless injured the vagal branches to such an extent that the pouch later did not respond to psychic stimuli.

Jemerin and Hollander state that nowhere in the work of Pavlov and Khigine did they indicate that they had carried out actual dissection to demonstrate the course of the vagi. Instead Khigine in his original thesis referred to Ellenberger and Baum (16) whose description and illustration he utilized. Jemerin and Hol-



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REPRINTS of the Editorial "Aids to Normal Bowel Function," "Amer. J. Dig. Dis.," March, 1939, J. A. Bergen, M.D., will be supplied on request.

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lander also stated that the Pavlov pouch technique was based upon the erroneous anatomical concept that only the ventral trunk runs along the lesser curvature, whereas the dorsal trunk courses along the greater curvature.

It must be remembered that Pavlov was highly conversant with the anatomy and physiology of the vagus nerve and its branches. With Khigine, Pavlov devoted three years to the anatomical and surgical studies which led up to the production of his pouch.

During the ten years in which I prepared demonstrations for Pavlov he was always much interested in the vagus nerves, and he always insisted on studying them whenever some dissection brought them into view. Regardless of what is shown in the diagrams published in his various papers, Pavlov always made the incision in such a way that one-tenth or never more than one-eighth of the incision went perpendicular to the branches of vagus nerves as shown in the dissections of Jemerin and Hollander (1). The incision in the mucosa was made so as to preserve the remainder of the nerve supply. Furthermore, and this is the important point, about a month after performing the operation, Pavlov would always test the animal for psychic secretion, and discard it if the pouch did not respond.

Anyone who will study Pavlov's published protocols will note that he usually made small pouches so as to be certain that the isthmus or the portion of serosa and muscularis and nerves cut was small; this is indicated by the relatively small amounts of secretion which he usually obtained and recorded. To obviate this difficulty, I simplified Pavlov's technique and made larger pouches. This was done by making an incision in the ventral wall of the stomach and completing the incision of the mucosa through the opening. This sectioned some vagal fibers in the ventral wall, but none elsewhere (10-18). Such pouches not only manifested a psychic secretion, but they secreted relatively large quantities of juice.

It should be emphasized that the crucial test for determining if one has made a true Pavlov pouch should not be an anatomic but a physiologic one, namely, one should test to see if the pouch will secrete in response to psychic influences. The observations of Hollander and Jemerin will serve to emphasize the importance of preserving the maximum amount of nerve supply to the pouch.

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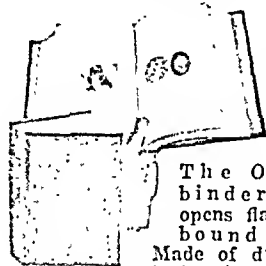
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MALKIN, J. I. AND MARKOW, H.

Analysis of the Comparative Results of Skin Testing with Cooked and Uncooked Foods. J. Allergy, 10:337, 1939.

A large series of allergic patients were skin tested with extracts of raw foods and extracts of the corresponding cooked foods in an effort to determine to what extent heating denatures foods. Seven hundred and eleven pairs of intradermal tests were done and in 652 (91%) instances, the reactions with the two extracts were considered equal. In 3.9% of the tests the raw extract yielded a positive test and the cooked one a negative one, while in 4.3% the cooked extract was positive while the raw one was negative. The authors believe that the differences between reactions with raw and cooked extracts is not sufficient to warrant any change in the present methods of preparation of allergenic extracts.

EHRENFELD, I., BROWN, A. AND STURTEVANT, M.

Allergy in the Pathogenesis of Peptic Ulcer. J. Allergy, 10:342, 1939.

A series of 75 patients with proven peptic ulcers were subjected to routine allergic studies. No relationship between ulcer and atopy could be es-

tablished. A group of 72 allergic subjects were then investigated for the incidence of peptic ulcer. A few patients among this group gave histories of gastro-intestinal symptoms which consisted chiefly of spasm of the stomach and duodenum. The incidence of urticaria and angioneurotic edema was higher among allergy patients having gastro-intestinal complaints. The authors conclude that allergy is rarely associated with peptic ulcer.

GERSHON-COHEN, J., SHAY, HARRY AND FELS, S. S.

Experimental Studies on Gastric Physiology in Man. IV. The Influence of Osmotic Pressure Changes of Salt and Sugar Solutions on Pyloric Action and Gastric Emptying in the Normal and Operated Stomach. Am. J. Roent. and Radium Therap., 40 (3):335-343, 6 figs., 1938.

The influence of duodenal osmotic change on gastric motility and on the action of the pylorus was studied roentgenographically. The standard test meal consisted of 2 oz. of barium sulfate in tap water, at or near body temperature, to which salt and sugar solns. of various osmotic tensions were added. For both normal and operated stomachs, the greater the hypertonicity of the test meal, the slower was gastric emptying.—E. H. Quimby (Courtesy of Biol. Abst.).

HEINANEN, N.

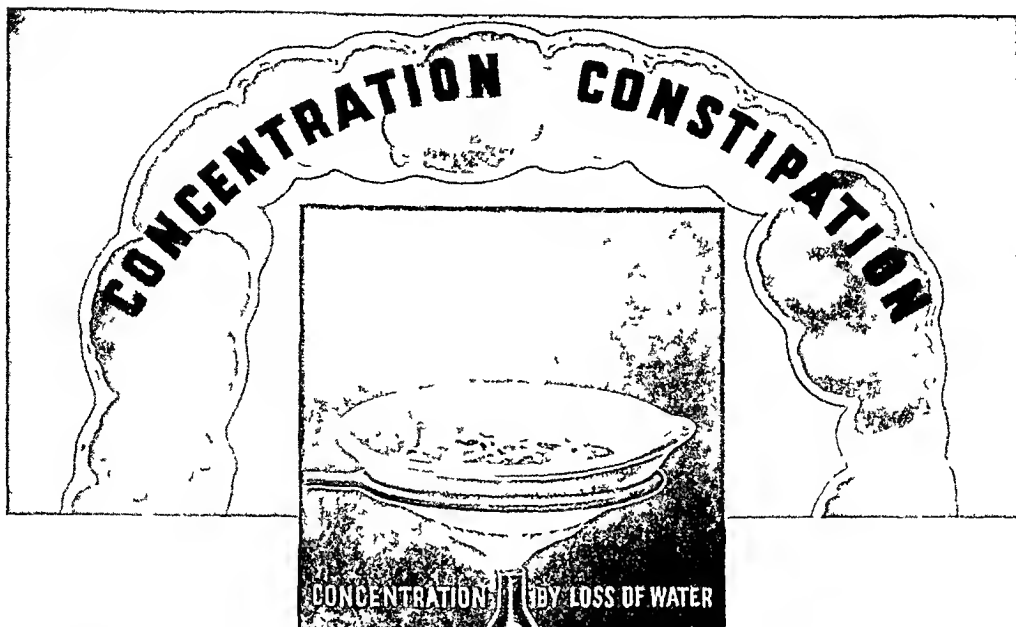
Welche Resultate gibt die interne. Behandlung der Ulkaskrankheit? Acta Med. Scand., Suppl. 89:327-331, 1938.

The late results do not correspond with those obtained under hospital treatment. This may be due to the type of patient (artisans) who cannot follow their dietetic treatments adequately.—J. F. Wilkinson (Courtesy of Biol. Abst.).

MACLACHLAN, P. L. AND HODGE, HAROLD CARPENTER.

The Influence of Cocaine Feeding on the Liver Lipids of the White Mouse. J. Biol. Chem., 127(3): 721-726, 1939.

Albino mice were given graded and increasing doses of cocaine hydrochloride per os. The livers were taken after 60 days and the lipids studied chemically and histologically. A vacuolar degeneration was observed in every case and an extensive fatty infiltration in nearly half the cases. Neutral fat and cholesterol increased greatly in the latter cases, the neutral fat more than the cholesterol. In contrast, the phospholipids showed a striking constancy, emphasizing the importance of these substances as true cellular constituents.—H. C. Hodge (Courtesy of Biol. Abst.).



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*Welch, P. B., and Kauders, F. H. The Physiologic Approach to the Correction of Constipation, South M J 31 709 (July) 1935

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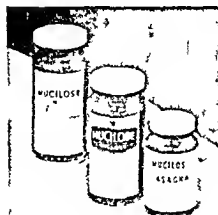
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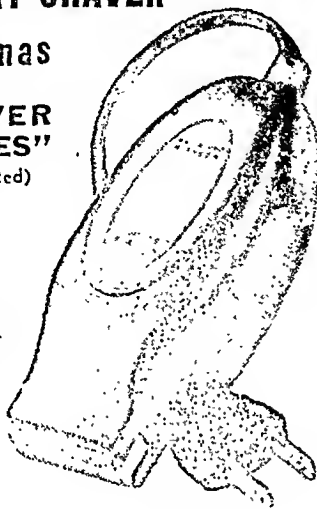
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CONNOTATIONS

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Denver, Colorado

Grases reported 188 cases of obturator hernia found in the literature between 1720 and 1890. Meyer states that 61 of these cases were reported prior to 1875. Englisch's textbook which appeared in 1891 stated that Hahn reported two cases in which the bladder was present in the hernia. Kronlein in 1890 described a strangulated obturator hernia which contained the uterus, ovary, tube, and a loop of small intestine. Rogner-Gusenthal observed a strangulated tube and ovary both of which were gangrenous. Chiene in 1870 recognized a portion of the ileum and the outer two-thirds of the left tube and the whole of the left ovary in a hernial sac.

According to Mueller, Ambrose Pare in 1558 drained an abscess from the knee and unexpectedly found a loose cartilage. In 1691, Pechlin, a Swedish surgeon described the symptoms accompanying this condition. Monroe in 1726, Simpson in 1736, and Morgagni reported similar cases. Benjamin Bell in 1787 advised amputation of the leg. He remarked: "The remedy is severe but is less painful and hazardous." Laennec in 1813 described the formation of these bodies. Larry in 1860 collected 170 cases submitted to surgery; 117 were successful, 33 died and 20 were failures. Recklinghausen reported the presence of loose bodies in case of arthritis deformans. Berry in 1894 removed 1047 free bodies from a joint which four years earlier had 50 similar bodies removed. The concretions surrounded a nucleus of cartilage and varied in size from a fine bead to a pea.

The older text-books of surgery, written by P. Franco as late as 1561 made no mention of lumbar hernia. In 1672, Pnul Barbette said "Experience has taught me that the peritoneum may rupture in its posterior aspect thus forming a hernia." Dolle is often credited as describing a lumbar hernia; however, there is nothing in his Latin writings to indicate his knowledge of this anomaly. Budgeon in 1728 described such a hernia, but there is some doubt as to whether his patient actually suffered from a lumbar hernia, for he describes his patient as presenting a congenital tumor in the region of the kidney, which ruptured at the age of 17 years. It has been suggested that the tumor was perhaps a spina bifida or hydronephrosis.

Gnrgangeot observed a strangulated lumbar hernia, and Ravnton in 1750 published a report of successful operation of a strangulated hernia. Petit is often given credit for describing the triangle through which lumbar hernias protrude. The writings of Petit makes no reference to anatomical data on this subject.

MELLANBY, J. AND SUFFOLK, S. F.

A Quantitative Investigation Into the Enterohepatic Circulation of Bile Salts in the Cat. Proc. Roy. Soc. (London) Ser. B., 126(844):287-302, 1938.

In a fasting cat about 95% of the total bile salt is contained in the gall bladder bile. The hepatic bile, continuously secreted by the liver, contains only traces of bile salt. In the fed cat the vol. and bile salt content of the hepatic bile shows a large increase while the gall bladder contains only a small quantity of relatively dilute bile. The removal of the small intestine causes an immediate fall in the cholic acid content of the hepatic bile to that found in the fasting cat. Bile salts are absorbed more rapidly from the ileum than from the duodenum and jejunum. A small amount of absorption occurs in the large intestine but the absorption of water takes place much more rapidly than that of bile salt. Consequently, the original conc. of bile salt may be increased fivefold in the unabsorbed bile. Bile salts injected into the blood are rapidly excreted in the hepatic bile. They are non-threshold substances in respect of the biliary apparatus. Bile salts

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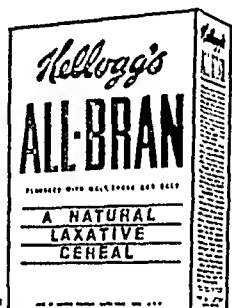
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are not stored in any tissue outside the enterohepatic system. The intravenous injection of secretin increases by 50% the volume of bile secreted by the liver. It has no effect on the total quantity of cholic acid contained in the bile; its action is therefore that of a hydrogogue. Stimulation (acetylcholine) or paralysis (atropine) of the parasympathetic nerves to the liver has no influence on the volume or cholic acid content of the bile. Stimulation of the sympathetic nerves to the liver (adrenalin) diminishes to a small degree the volume of the bile secreted but augments the total amount of cholic acid contained in it. The sympathetic nerves may stimulate the formation of cholic acid from some inactive precursor by the liver cells. After removal of the bile from a fasting cat, 2/3 of the cholic acid is resynthesized in 2 days if the animal feeds well. In the absence of eating no synthesis of cholic acid takes place. A cat contains approximately 100 mg. of cholic acid per kg. of body weight. A rat contains approximately 25 mg. cholic acid per kg. of body weight. The rate of flow of bile per unit of body weight is about 6 times as great in the rat as in the cat.—Authors (Courtesy of Biol. Abst.).

SECKEL, H. P. C.

The Influence of Various Physiological Substances on the Glycogenolysis of Surviving Rat Liver. Methods; Influence of the Bile Salts. Endocrinology, 23(6):751-759, 2 figs., 1938.

Lesser's method of estimating the "diastatic efficiency" of frog liver lobes was modified for warm blooded animals by determining the 60 minute decrease in glycogen of rat liver slices surviving in a buffer solution at 37° C. The effect on this system of various concs. of 2 bile-salt preparations containing different properties of Na glycocholate and taurocholate was studied in 62 experiments. By expressing the "bile-salt glycogenolysis" in terms of + and — deviations from "bile-salt-free glycogenolysis" a bi-

phasic curve in bile-salt glycogenolysis was obtained. The positive phase of this curve occurred at low concs., the negative phase at high concs. The physiological action of the surface-active bile salts on the intracellular fixation of the glycogenase to the protein boundary structures of the liver cells is discussed. The relationships of the findings to Forsegren's daily cycle of the liver function, artificial and pathologic obstructive jaundice, and von Gierke's glycogen storage disease is considered.—D. Permer (Courtesy of Biol. Abst.).

HOREJSI, J. MECL, A. AND SPISAROVA, J.

The Metabolism of Aminoacids and Liver Functions. Acta Med. Scand., 96(2/4):217-230, 4 figs., 1938.

Urea concentration and amino-N are of no value in hepatic function determinations, while the ammonia excretion can only be used with caution. The Glycine tolerance is of value. Insulin has a similar but less effect on amino-N to that on blood sugar. Urea excretion is valuable in estimating hepatic function, a rising excretion after glycine and a falling neogenic quotient are a favorable sign. There is reasonable agreement with results obtained by other tests for hepatic function.—J. F. W. (Courtesy of Biological Abstracts).

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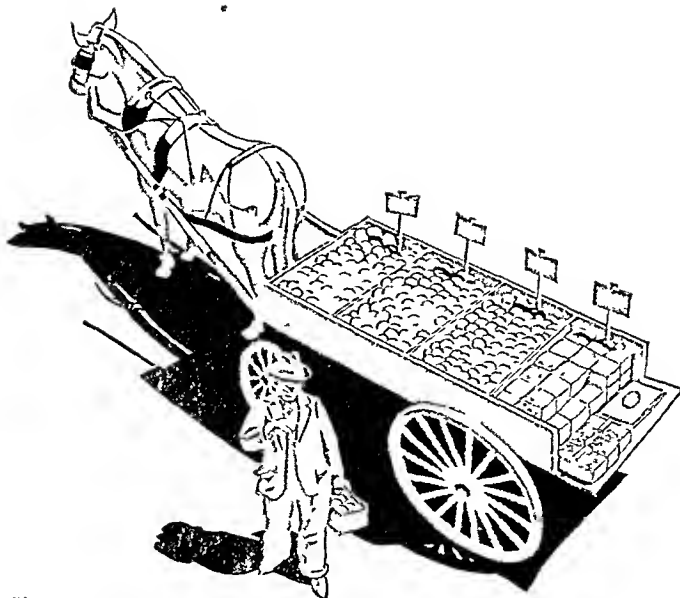
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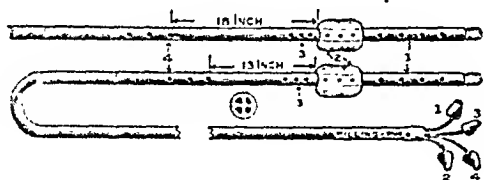
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VELICK, SIDNEY F., WHITE, JULIUS AND LEWIS, HOWARD B.

The Synthesis of Dicholyleystine and Cholyleysteic Acid. J. Biol. Chem., 127(2):477-481, 1939.

The peptide, dicholyleystine, has been synthesized and its oxidation to cholyleysteic acid described. The compounds are of interest in view of the suggestion that the conjugation of cholic acid with cystine may occur in the biological synthesis of taurocholic acid.—J. White (Courtesy of Biol. Abst.).

CONNOTATIONS

H. J. SIMS

Denver, Colorado

DeBeule recognized and named the "en w" type of incarcerated hernia. Lnuenstein in 1894 first described this type of hernia. Maydl in 1895 described 2 cases of strangulated hernia; in the first case, the distal end of the hernia remained in the abdomen, and the sac contained the appendix. In the second case, the Falloppian tube was involved in the same manner as the appendix. In both instances, the distal ends of the organs were gangrenous, and that part contained within the sac showed only mild circulatory disturbances. Maydl used the term "retrograde incarceration" to describe the condition. Schmidt in 1890 described such a formation in a strangulated umbilical hernia. Friedman in 1913 reviewed the cases reported in the literature.

Hey in 1814 used the name, infantile hernia, to describe an encysted hernia. It has been suggested that he used the term because his description was drawn from an infant with such a hernia. Cooper in 1827 described this variety of hernia and is usually given credit for its recognition.

Erythromelalgia was first described by Wier Mitchell in 1872. In 1878 he used the term erythromelalgia, signifying a red painful limb.

The production of an artificial communication between the venous cavity and portal vein for the relief of portal cirrhosis was first described by Eck, a Russian surgeon, in 1877. His work was confined to animals. Vidal of France, carried out this procedure on man. The patient lived four months and died of cardiac disease. Rosenstein performed the second operation with temporary relief.

Primary malignant disease of the appendix was recognized by Merling in 1838. The incidence occurred in a young girl dying from general peritonitis. Kalszeck in 1875 and Rokitsky in 1867, each reported a case. In the absence of a microscopic examination and an inadequate description, the diagnosis is problematical. Wenzel-Gruber in 1875 observed a cyst of the appendix. Lufforgue in 1893 found only 17 tumors of the appendix in the literature. Among these there were 1 lipoma, 1 myoma, 2 lymphadenomas and 2 hydatid cysts. Murphy recorded 2 cases, and Oviatt and Carson a single case of myoma of the appendix. Kelly in 1905 reported a fibroid tumor of the appendix.

BRENNAN, W. R.

Variations in the Reaction of Chicks to Different Methods of Administering Androgens. Endocrinology, 24(1):55-62, 1939.

Using White Leghorn cockerels, it was found that the relative effectiveness of oreton and oreton-B, as measured by comb growth, was the same whether injected subcut. or intraperit. Both were more efficient administered subcut., but comb growth was always greater with oreton-B. Androstenedione and dehydroandrosterone were less effective than oreton or oreton-B. Androstenedione plus oreton-B was more effective than oreton plus oreton-B. Body weight was essentially the same in both control and injected chicks until after cessation of injections; then controls became progressively heavier. Baby cockerels given oreton plus oreton-B for the first 5 days after hatching grew on the 7th day. Birds given oreton-B alone but in

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an amount equal to combined dosage of oreton plus oreton-B crowded on the 5th day of age.—D. Permar (Courtesy of Biol. Abst.).

RENTZ, ED.

Über den Einfluss der vagusreizung auf die Bewegungen des Dickdarms. Arch. Exp. Path. u. Pharmacol., 191(2):172-182, 12 figs., 1938.

Studies of the guinea pig and rabbit colon in situ with recording by Straub's technique showed that the proximal colon responded in essentially the same manner as the small intestine to electrical vagus stimulation. Results were less certain with the distal colon. Often, after a latent period of a few minutes, there was a general transitory augmentation of function. Disturbed rhythm in the fatigued colon was made normal, or stopped peristalsis was overcome. A reaction like that of the small intestine to electrical vagus stimulation was seldom seen. The proximal colon, like the small intestine, is evidently under the influence of the vagus. In the distal colon such influence could not be recognized, although the different function of this section of the gut was modified, but did not always alter itself in the same way in response to electrical stimulus.—C. S. Leonard (Courtesy of Biol. Abst.).

QUACKENBUSH, FORREST WARD, PLATZ, BLANCHE RHISING AND STEENBOCK, HARRY.

Rat Acrodynia and the Essential Fatty Acids. J. Nutrition, 17(2):115-126, 1939.

On a basal diet of purified casein, glucose and salts, supplemented with carotene, calciferol, synthetic B. and riboflavin, rats developed a severe dermatitis which de-

veloped in over 500 animals within 4 to 5 weeks and which took on an acute and a chronic form; complete healing of either was obtained by the adm. of peanut oil or wheat germ oil. By a standardized technique cures were obtained with $\frac{1}{2}$ drop of wheat germ oil, corn oil, or Wesson oil, 10 drops of coconut oil and 25 drops of butterfat. The lesions were not prevented or cured by a supplement of 10% hydrogenated coconut oil. The unsaponifiable fraction from wheat germ oil was devoid of potency. The ethyl esters prepared from the soap fraction contained all of the activity. When the unsaturated fatty acids were fractionally crystallized from acetone, the highest potency was obtained with a fraction separating between -50 and -75° C. One-half drop of ethyl linoleate per day was curative.—Authors (Courtesy Wister Bibl. Serv.).

DHAYAGUDE, R. G. AND KHADILKAR, V. N.

True Achlorhydria and Anaemia. Indian J. Med. Res., 26(3):705-730, 1939.

A study of 75 cases of achlorhydria by fractional test-meal analysis was made. Majority of the cases showed varying grades of anaemia. To find out whether achlorhydria was true or false subcut. inj. of 0.5 cc. of histamine acid phosphate (B.D.H.) was given after the fasting contents were taken out. 11 out of 75 showed free acid in fasting contents when the test was repeated. 25 showed free acid after histamine stimulation. Out of 75 cases of achlorhydria 39 were found to be cases of true achlorhydria, more than half of these were cases of Addison's pernicious anaemia or subacute combined degeneration of the cord, 4 Witt's anaemia, 3 associated with ankylostom infection and 5 of pellagra. The remaining were single instances of malaria, syphilis, cystitis, asthma and dyspepsia where the achlorhydria was probably accidental.—Authors (Courtesy of Biol. Abst.).

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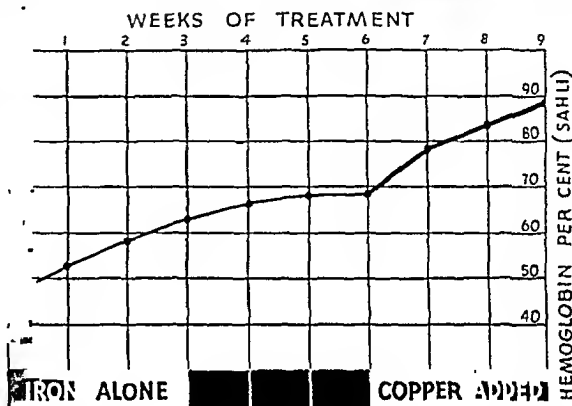
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*Am. J. Med. Scien., 6:182, 1931. Lyon, B. B. Vincent.

**Arch. Int. Med., 38:647, 1926. Am. J. Surg., 7:455, 1929.

IVY, A. C.

***J. Lab. & Clin. Med., 19:567, 1934. CoTui, F. W.

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